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## THE RELATIONS OF SCAPULAR TYPES TO PROBLEMS OF HUMAN HEREDITY, LONGEVITY, MORBIDITY AND ADAPTABILITY IN GENERAL †

WILLIAM W GRAVES, M D  
ST LOUIS

"Heredity is a convenient term for the genetic relation between successive generations"—"Heredity determines the individual life"—J Arthur Thomson

"Life is short and the art long, the occasion fleeting, experience fallacious and judgment difficult"—"It is the business of the physician to know, in the first place, things similar and things dissimilar " Thus spoke the Father of Medicine

Human experience teaches that like tends to beget like in the propagation of plants and animals. Yet no two are exactly alike. Resemblances, similarities and differences are found among individuals of any species, but Nature has produced no duplicates. Each individual is truly the first and last of its particular kind. However close may be the kinship of individual A and individual B, they are never equal in their natural endowments. A is always more or less competent than B in structure and function, always more or less competent than B in capacities for adaptation. The relations of structure, function and environment are so close that we cannot think of the one without the other. Structures and functions, in their combined and reciprocal relations, make up the individual organism, and it is with them that it struggles for existence, adapts itself excellently, well or poorly to an ever varying environment and finally perishes. Because no two human beings are alike, because they differ in natural endowments and consequently in structures, functions, acquirements and total makeup, because they differ in their innate capacities for adaptation, the individual is a fundamental and universal problem. Every day observations reveal glaring structural and functional differences, similarities and inequalities in individuals of any species, and this is especially true of the human. As physicians, we do not always realize that such of these as are inherited may be utilized as conditional indices of a person's adaptability, of his capacities for health or disease, or even of his

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\* From the Department of Nervous and Mental Diseases, St Louis University School of Medicine

many or few years of life Among the inherited differences, similarities and inequalities abounding in the structures of the human species, and among those readily recognizable in the living are certain variations of the shoulder-blade

The scapula is one of the distinctive bones of the body, is composed of many varying characteristics and is of unusual functional importance Prior to investigations, beginning in 1906, it had received comparatively little consideration by anatomists, anthropologists and clinicians Nevertheless, its general form and some of its special features had been described, its relation with muscles and contiguous bones investigated, its range in variation emphasized, Broca,<sup>1</sup> Mivart,<sup>2</sup> Turner,<sup>3</sup> and Dwight,<sup>4</sup> some racial and sex differences pointed out, Broca,<sup>1</sup> Livon,<sup>5</sup> Dorsey<sup>6</sup> and Flower,<sup>7</sup> its comparative anatomy considered, Mivart,<sup>2</sup> Turner,<sup>3</sup> Dwight,<sup>4</sup> Ranke<sup>8</sup> and Schuck,<sup>9</sup> some of its indices established, Broca<sup>1</sup> and Martin<sup>10</sup> and its ossification and growth from fetal to adult life described But a scapula was still a scapula It was merely one among many bones of the body, and aside from its importance to proper function of the shoulder girdle and upper extremities, it had attained no particular significance

Prior to my investigations, no one, so far as I know, had made comparative studies of the many and varying characteristics of human scapulae and classified them It is the purpose of this paper to recall observations leading to the classification of human scapulae into readily recognizable types, to mention the scope, and to summarize some of the results of those investigations fundamental to an appreciation of the relations of scapular types to problems of human heredity, longevity, morbidity and adaptability in general

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1 Broca, P Sur les indices de largeur de l'omoplate chez l'homme les singes et dans la serie mammiferes, Bull Soc d'anthrop de Paris **1** 67, 1878

2 Mivart, St G On the Appendicular Skeletons of the Primates, Phil Tr Roy Soc, London **156** 299-429, 1867

3 Turner, W Report on the Human Skeletons Part 2 Reports of the Chall Exp Zoology **16** 1886

4 Dwight, Thomas The Range of Variation of the Human Shoulder Blade, Am Naturalist **21** 627, 1887

5 Livon, M De l'omoplate et de ses indices de largeur dans les races humaines, These inaug, Paris, No 346, 1879

6 Dorsey, G A Observations on the Scapulae of North West Coast Indians, Am Naturalist **31** 736, 1897

7 Flower, W H The Scapular Index as a Race Character in Man, J Anat & Physiol **14** 13, 1879-1880

8 Ranke, J Zur Anthropologie des Schulterblattes, Kor-Bl f Anthrop **34** 139, 1904

9 Schuck, C Das Schulterblatt des Menschen und der Anthropoiden (Aus Band XL [der dritten Folge Band X] der Mitteilungen der Anthropologischen Gesellschaft in Wien), Wien, 1910

10 Martin, R Lehrbuch der Anthropologie in systematischer Darstellung Jena, 1914, p 904-907, p 975-980

On Sept 18, 1906, while making a routine physical examination in the neurological clinic of the St Louis University School of Medicine, of A R, a boy, aged 7 years, I was impressed with the peculiar contour of the vertebral borders of his shoulder-blades. Each vertebral border was distinctly concave (the right more than the left) from the mergence of the spine of the scapula with the vertebral border, to a point slightly above the inferior angle of the bone. These borders and the inferior angles stood out prominently, like wings. The vertebral borders were unusually far apart and their general course paralleled the spinal axis.



Fig 1—The R1 family, Dec 2, 1909, approximately three years after initial observation. Father 46, mother 42, A 10, C 8, and L, 5½ years of age, respectively. A similar view of the children 10 years later is shown in Figure 4.

The boy's neck appeared unusually long. His shoulders were hanging, drooping downward and forward, and the right was lower than the left. The thorax was well formed, though shallow and somewhat narrowed about the lower costosternal junction. The clavicles took a distinctly horizontal course, the abdomen was unduly prominent about its lower half and the body attitudes were those of extreme sluggishness. His stature and weight were much less than the average, and his muscle development was meager without evident atrophy. He was able to assume normal attitudes, to elevate and approximate his shoulder blades in a proper manner and to execute all movements with strength propor-

tionate to muscular development His mother, aged 39, disclosed vertebral borders more concave than those of the patient and poor general development, whereas his father, aged 43, disclosed convex vertebral borders and good general development The younger children, a boy, aged 5 years, and a girl aged 3 years, disclosed concave vertebral borders, and in general makeup the three children resembled the mother rather than the father (Fig 1)

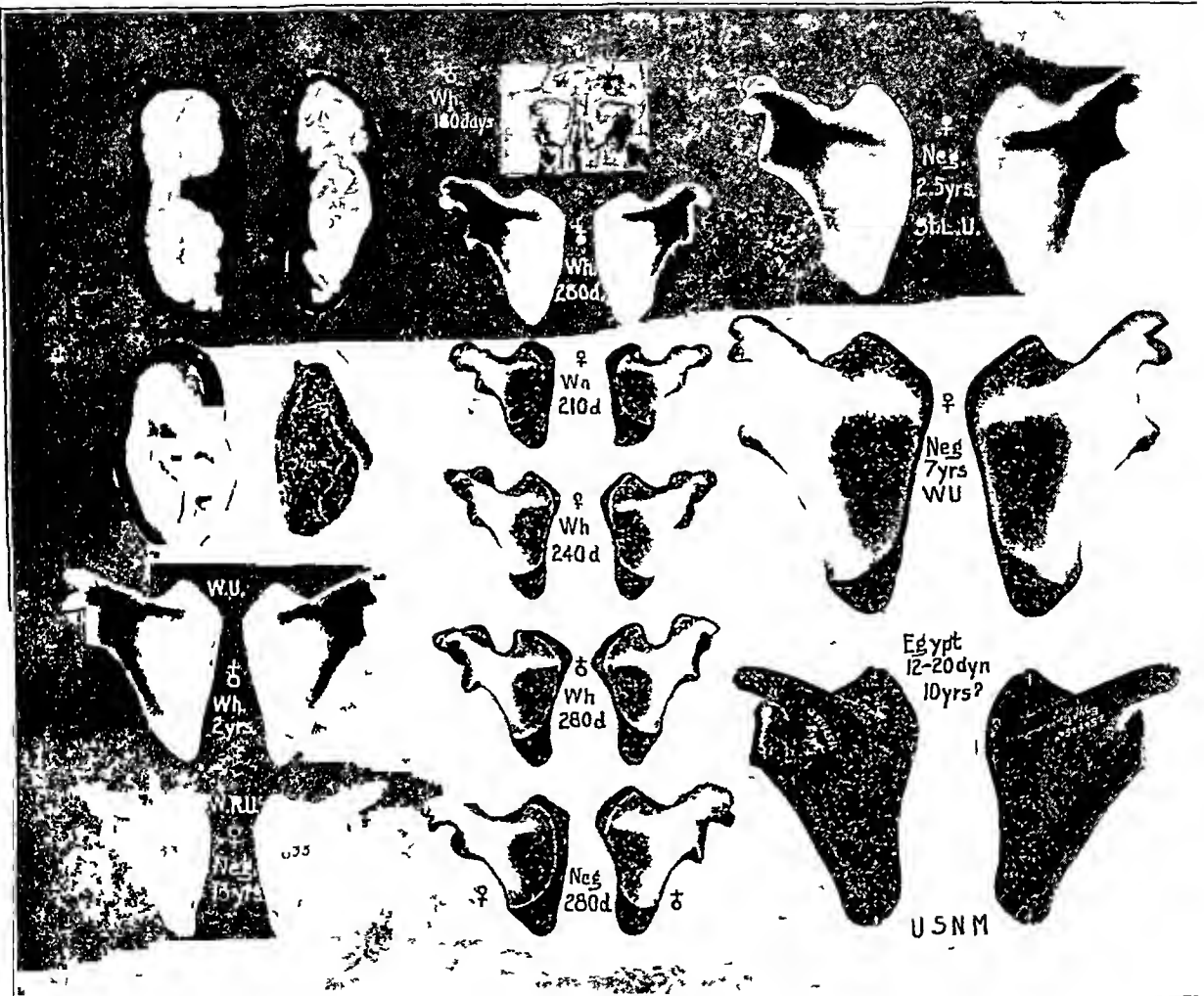


Fig 2—Convex, straight and concave scapular types from approximately tenth fetal week to thirteenth year of life Note the varying relation of bone to cartilage in the roentgen-ray figures and in those marked 633, and the loss of cartilaginous glenoid, acromion, vertebral border and inferior angle regions in the Egyptian Compare with Figure 3

#### CLASSIFICATION

Since the vertebral border of the human scapula had been described, and usually pictured as having a more or less convex outline similar to that found in the father of the R1 family, the finding of concave ver-

tebral borders in the mother and the three children, associated with rather poor general development, led to further observations on scapular-vertebral-border formation on living subjects and to intimate studies of skeletal and fetal scapulae. Observations on living subjects soon revealed the existence of a limited range in variation of scapular vertebral borders, from markedly convex to markedly concave. In some persons I found markedly, in some moderately, in some slightly concave, in some markedly, moderately or slightly convex, in others vertebral borders neither convex nor concave but intermediate in contour, seemingly straight or nearly so. Comparative studies of living and similar studies of skeletal and fetal material have led to the classification of human scapulae into convex, straight and concave types (Figs 2, 3 and 5).

The classification is based on the relation of a straight line to the greater portion of the vertebral border below the scapular spine, but fundamentally it is based on a combination of the anatomic and architectural features peculiar to each type. In my first communication<sup>11</sup> in 1910, I pointed out five or more features common to straight and concave types. That study was based on only 198 mature skeletal scapulae, of which 61 per cent were convex, 26 per cent straight and 13 per cent concave. In a recent comparative study of 1,219 mature bones, it has been clearly shown that the concave and the straight have twelve or more features in common, and, therefore, constitute a variant type con-

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11 Graves, W. W. The Scaphoid Scapula—a Frequent Anomaly in Development of Hereditary, Clinical and Anatomical Significance, *M Rec* **78** 861-873, 1910, The Clinical Recognition of the Scaphoid Type of Scapula and Some of Its Correlations, *J A M A* **55** 12-17 (July) 1910, *J Missouri M A* **7** (Dec) 1910, Some Remarks on the Scaphoid Scapula and Its Syndrome, *Tr Nat Assn Study Epilepsy* **8** 56 (June 16) 1911, The Scaphoid Scapula Syndrome, Its Connection with Syphilis in the Ascendants, *Interstate M J* **18** 109-116, 1911, transl. *Deutsch Ztschr f Nervenhe* **41** 247-257, 1911, Scapula scaphoidea eine häufig vorkommende Anomalie des Schulterblattes, Ihr Zusammenhang mit Syphilis in der Aszendenz, *Med Klin* **8** 208-301, 1911, Einige Bemerkungen über die Skaphoidskapula und ihre Begleiterscheinungen (Translation of Ref No 3 by V Kollert) *Wien klin Wchnschr* **25** 245-258, 1912, Remarks on the Scaphoid Scapula and Its Syndrome, the Connection with Syphilis in the Ascendants, *J Cutan Dis incl Syph* **31** 241-245, 1913, The Age Incidence of the Scaphoid Type of Scapula—Its Bearing Upon Problems of Racial Morbidity, in *Contributions to Med & Biol Research*, dedicated to Sir William Osler, Vol 1, New York, Paul B Hoeber, 1919, pp 525-532, An Appeal for Embryos and Foetuses, *J A M A* **73** 1788 (Dec 6) 1919, Discussion—The Scaphoid Type of Scapula, *Am J Syphilis* **4** 478, 1920, The Types of Scapulae—A Comparative Study of Some Correlated Characters in Human Scapulae, *Am J Phys Anthropol* **4** 111, 1921, Observations on Age Changes in the Scapula—A Preliminary Note, *Am J Phys Anthropol* **5** 21, 1922, The Age Incidence of Scapular Types—Its Possible Relation to Longevity, *Trans Am Assn Life Ins Med Directors*, 1923.



trasting vividly with the convex<sup>12</sup> These comparative studies have justified combining the straight and concave forms and designating them the *scaphoid type* (Fig 5) Further justification was found in the fact that persons in whom the vertebral border was classified straight often disclosed deviating characteristics in total makeup similar to, although, as a rule, less marked than in those in whom it was found to be concave

Because the scaphoid (concave or straight) was found with relative frequency in all periods of life, because more or less convexity of the vertebral border had been considered by anatomists a characteristic of the so-called "normal" or "average" scapula in man, and because mammalian families below man, as a rule, disclosed more or less convex scapular vertebral borders, I formerly considered the scaphoid type an anomaly in development, and I have in my writings repeatedly referred to it as such<sup>11</sup> Further investigations of living and skeletal material of man and of vertebrate skeletal material in general, and a better appreciation of the range of variation in the structures and functions in man's total makeup, have convinced me that it is erroneous to consider the scaphoid type (concave or straight) an anomaly It would be equally valid to consider the convex an anomaly for the reason that each scapular type (convex, straight or concave) is fundamentally a combination of morphologic and architectural features peculiar to human scapulae Therefore, it is erroneous to consider any one of the three types as the "normal" or the "average" type Further reasons for this conclusion will presently become obvious

#### THE RELATIONS OF SCAPULAR TYPES TO PROBLEMS OF HEREDITY THEIR PRIMAL OR GERM-PLASM ORIGIN

Observations on living and skeletal material from birth to old age show the presence of convex, straight and concave scapular types in all period of life in varying degrees and percentages

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<sup>12</sup> The chief characters common to the straight and concave types contrasting with similar characters in the convex are as follows (1) Thickness of the vertebral border, (2) "vertebral-border buds" or processes varying in location, size and number, (3) "vertebral-border remnants," meaning a part of the vertebral-border system (lips and intermediary surface) morphologically more or less complete, (4) three scapular indices Broca's scapular and infraspinous indices and Hrdlička's index, (5) the degree of angle formed by the long scapular axis with the general direction of the scapular spine ("long scapular axis-spinal angle"), (6) the relation of the vertebral border below the scapular spine to a straight edge, (7) the relation of the inferior border to a horizontal, or to a vertical when the long scapular axis is vertical, (8) the relation of the teres major process to axillary border, (9) the relation of the long axis of glenoid to long scapular axis, (10) the character of the inferior-angle region, (11) the densities of the bones to transmitted light, (12) the densities of the bones to the roentgen-ray, (13) muscle markings of bones in approximately the same age periods, (14) average weight of bones having similar long axis measurements in approximately the same age periods

Dissections of fetal scapulae in approximately the tenth week of development (when the human scapula is mainly cartilaginous) and onward in prenatal life, show convex, straight and concave types (Fig 2)

Observations on the living in our population, regardless of age, sex, race, stock, environment, occupation, social level, health, disease, type or build show the presence of convex, straight and concave scapular types in varying degrees and percentages



Fig 3—Mature scapular types in apes and in ancient and modern man. Ossification is complete in all, except in one gorilla and in those marked  $\tau$  and in orang-utan marked O. Immature gorilla, orang-utan and human scapulae show similar morphology. (Compare Figs 2 and 3). Cartilaginous vertebral border of scapula in right lower corner was removed before being roentgenographed. (The scapulae of apes, Egyptians and American-Indians were photographed by permission of Drs A Hrdlička and G S Miller, Jr [U S National Museum], and those numbered 633, 575, 599 and 181 were photographed by Prof T W Todd [Hamann Mus W R Med School])

Observations on approximately 3,500 skeletal scapulae representing the several races of man, beginning with modern and going back as far as pre-dynastic Egyptian, show the presence of convex, straight and concave types in all races thus far investigated. Similar types are also found in several mammalian families below man, and particularly in the orang-utan, gorilla and chimpanzee<sup>11</sup> (Fig. 3).

The number and percentages of convex, straight and concave scapular types, from mixed-stock dissecting room material in 1,219 mature bones, whose bearers ranged in years from under 25 to over 96, with an average age of approximately 50 years were found to be as follows:

	Mature Bones	Percentages
Convex	663	54.3
Straight	320	26.2
Concave	236	19.5

The scapulae of ancient man thus far found in sufficient numbers (unknown average age), when classified, yielded the following numbers and percentages:

Twelfth to Twentieth Dynasty Egyptians (U. S. National Museum)<sup>11</sup>

	Mature Bones	Percentages
Convex	20	44.4
Straight	13	28.8
Concave	12	26.8

Pre-Columbian Peruvian Indians (U. S. National Museum)<sup>11</sup>

	Mature Bones	Percentages
Convex	32	66.6
Straight	11	22.9
Concave	5	10.5

Pre-White Pueblo Indians (U. S. National Museum)<sup>11</sup>

	Mature Bones	Percentages
Convex	77	69.3
Straight	22	19.8
Concave	12	10.9

The presence and percentages of the three types in the remains of ancient and modern man, the finding of identical scapular types in prenatal and postnatal life periods, regardless of sex, race and environmental influences, and the finding of similar types in mammals below man, justify the inferences that all races of man at all times have shown similar variations and types, and that the origin of scapular types in man is primal.

#### THE INHERITANCE OF SCAPULAR TYPES—"NORMAL" AND "ALTERED"

Positive proof of the primal or germ-plasm origin of scapular types is found in comparative studies of parents and progeny. Such origin was clearly indicated in the observations on the R. 1 family, and one need only examine the members of his own family to find indubitable evidence of the fact. Comparative studies of as many members as were

accessible in approximately 1,000 families, representing two, three, four and five generations have shown that the resultant scapular types in the progeny were usually dependent on scapular type matings, i e., the kind of scapular types possessed by parents. These studies have led me to the conclusion that in *no single recognizable morphologic or functional trait or characteristic of human inheritance, with the exception of definite racial characteristics, do the progeny more frequently and more closely resemble each other and one or both parents than in shoulder-blade types*. Under "normal" circumstances the transmission of scapular types, with but few exceptions is found to be as follows. Similar scapular-type matings (convex + convex, or concave + concave) produce similar scapular types in the progeny, dissimilar scapular-type matings (convex + concave) produce the scaphoid type in varying degrees (from concave to straight) in the progeny. The chief exceptions to these findings thus far noted appear to be due to occasional examples of atavism, or to the occasional presence of some disease or other poison factor in both parents. When only one child in a family of several children discloses a scapular type differing from that found in both parents, such a finding is construed as an example of atavism. When most, or all of the several children disclose types differing from those possessed by both parents, such findings are construed as evidence of altered scapular type inheritance. Considering the possible degrees of convexity or concavity (variations) in vertebral-border-contour formation in scapular type matings, the resultant scapular types in the progeny seem to be examples of *blending* rather than of *mendelian* inheritance, but my investigations are wholly insufficient to warrant at this time a definite conclusion one way or the other. Nevertheless, through family studies indubitable proof of the foregoing inference, i e., the primal, or germ-plasm origin of scapular types, has been found. This inference, it will be recalled, was based on the following ascertained and readily demonstrable facts: (1) the presence and relative percentages of each scapular type in the remains of ancient and modern man, (2) the presence of similar scapular types in some mammals below man, (3) their presence in all prenatal and postnatal periods from the tenth fetal week onward, and (4) their presence in varying degrees and percentages in all social levels represented in our population, regardless of age, sex, race, type build or environmental influences. Therefore, the finding of any scapular type (convex, straight or concave) in any person justifies the conclusion that it is innate with him, normal to him—a morphologic expression of his germ-plasm inheritance—even though the germ-plasm from which he developed may have been altered by disease toxins and possibly by some other poisons.

My observations thus far show that the frequency of "altered" is practically negligible when compared with the frequency of "normal"

(unaltered) germ-plasm inheritance in reference to scapular types I have found thus far no disease other than syphilis or other poison, capable of altering scapular type inheritance, but Reye<sup>13</sup> believes that alcoholism and tuberculosis in parents with convex types may have similar effects. However, he did not fully appreciate the necessity of examining both parents, as well as all of the progeny.

Several workers, notably Draeseke,<sup>14</sup> Reye,<sup>13</sup> Cunningham,<sup>15</sup> Warburg,<sup>16</sup> Bruckner,<sup>17</sup> Hosteing,<sup>18</sup> Thielke,<sup>19</sup> Balli,<sup>20</sup> Ravold,<sup>21</sup> Lance<sup>22</sup> and many others have construed my writings to mean that syphilis is the only cause of the scaphoid and is, therefore, a sign of congenital syphilis, or of syphilis in the ascendants. No assumptions could be further from the truth,<sup>11</sup> but there is some foundation for them in the fact that I at one time erroneously accepted the convex as the "normal" or "average" type in man and that, for good reasons, repeatedly emphasized syphilis as one factor that may alter scapular type inheritance in the progeny of convex-scapular-type matings.<sup>11</sup> Whether this disease in both parents having convex scapulae, has altered scapular type inheritance in their progeny can be determined only by comparative anthropometric and clinical studies. Such studies have not been recorded by any of the authors just mentioned, except Reye,<sup>13</sup> and his findings are in accord with mine in showing that altered scapular type inheritance is present in the progeny of some syphilitic parents having convex scapular types, but by no means in the progeny of all such parents. Whether a scapular type in a given individual is part of his "normal" or "altered" inheritance can be determined only by comparing him with the other members of his generation, with his parents and, when possible, with his more remote

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13 Reye, E. Untersuchung über die klinische Bedeutung der Scapula scaphoidea (Graves), *Ztschr f d Erforsch u Behandl d jugendl Schwachsinn*, Jena **5** 392-411, 1912.

14 Draeseke, Dr. Zur Kenntnisse der Scapula scaphoidea (Graves), *Ztschr f d Erforsch u Behandl d jugendl Schwachsinn*, Jena **6** 4, 1912.

15 Cunningham, Ruby L. The Scaphoid Scapula. A Normal Variation in Man, *Arch Int Med* **10** 589-596 (Dec) 1912.

16 Warburg, F. Ueber Scapula scaphoidea, *Med Klin* **9** 1851, 1913, Ueber Vorkommen und Bedeutung der Scapula Scaphoidea, *Berl klin Wchnschr* **2** 31, 1919.

17 Bruckner, Dr. Ueber die scaphoide Form des Schulterblattes, *Jahrb f Kinderh* **28** 291-296, 1913.

18 Hosteing, J. M. J. Contribution a l'etude de l'omoplate scaphoide et de ses connexions pathologiques, *These inaug*, Bordeaux, 1913, No 76.

19 Thielke, R. Zur Kenntnis der Scapula scaphoidea, *Inaug Diss der Albertus Universität zu Königsberg*, Königsberg, E. Rautenberg, 1913.

20 Balli, R. Il margine "rachion-metagonion" della scapola suo valore clinico, suo significato biologico, morfologico e fisiologico, Modena, 1917.

21 Ravold, A. Heredosyphilitics and Their Detection, *Illinois M J*, March, 1911.

22 Lance, M. L'omoplate scaphoide, ses connexions pathologiques ses rapports avec la syphilis hereditaire, *Gaz de hôp de Par* **85** 916-919, 1912.

ascendants We do not yet know the frequency with which syphilis or other poisons do or may alter human parental germ-plasm, but the finding of altered scapular type inheritance in the progeny of some syphilized convex scapular type matings appears to be the first conclusive evidence of the fact <sup>23</sup>

BIOLOGIC STANDARDS    CONDITIONAL MORPHOLOGIC INDICES    THE  
RELATIONS OF SCAPULAR TYPES TO PROBLEMS OF  
ADAPTABILITY IN GENERAL

Every day observations reveal biologic inequalities—inherited variations in structures, functions, total makeup and fitness in human beings—but we have found as yet no standard better than the ascendants and collaterals for measuring such inequalities, nor are we likely to find such Since scapular types show unusually frequent relations to heredity, they are useful conditional indices of the constitution of man They are not, however, standards with which we may measure man, any of his structures, any of his functions A particular scapular type is only one part of an individual's inheritance, hence it is a conditional, not an absolute, index The worth of any inherited feature as an index can only be determined by considering the number and degree of inherited variations coexistent with it The usefulness of scapular types as conditional morphologic indices is indicated by their relations to the attributes of an ideal in total makeup and adaptation We constantly define and utilize the attributes of such an ideal when we so readily classify human beings as "weak" or "strong" and as "excellent," "good" or "poor" types The attributes of a practical ideal appear to be good degrees of symmetry, proportion and harmony in total makeup and good degrees of adaptation in structures and functions the same in human beings as in all living things Now a consideration of these attributes in our study of the whole individual will usually enable us to discern his nearness to, or remoteness from, such an ideal Human beings possessing

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<sup>23</sup> Clinical observations of many physicians and the original investigations of E Fournier (*Syphilis Hereditaria Tarda*, Ger Trans by K Reis, 1908), in reference to the frequent occurrence of deviations in the progeny of syphilitic parentage and the original studies of Paul on "The Products of Conception in Lead Workers" (*Arch gen de med* **15** 513-534, 1860), clearly indicate the harmful effects of both syphilis and lead on human germ-plasm That the germ-plasm of lower forms can be altered by chemicals and other agents is conclusively shown in the results of investigations in recent years by many workers and among these may be mentioned Bardeen (*J Exp Zool* **4** 1-44, 1907), Tower (*Pub Carnegie Inst*, 1906), Watson (*Brit M J*, Oct 28, 1905), MacDougal (*Botan Gaz* **51** 241-257), Stockard and Co-Workers (*J Exper Zool* **26** 119-226, 1918, *Proc Am Phil Soc* **62** 31, 1923), Cole & Bachhuber (*Proc Soc Exper Biol & Med* **12** 24-29), Pearl (*J Exper Zool* **22**, 1917, part 1, 125-164, part 2, 165-186, part 3, 241-310), Weller (*J Med Res N S* **28** 271, 1915)

these attributes to a good degree disclose "the healthy mind in the healthy body," and they are readily recognized as belonging to the better types of the race. They seem to be endowed with such capacities that they adapt themselves well to varying environment, resist disease, survive and often attain long life. As physicians we seldom come in contact in a professional way with these types, with the "near to the ideal" in total make up and adaptation. Our medical and social problems are mainly with those types disclosing definite asymmetry, disproportion, disharmony and more or less defective adaptation of structures and functions. It is usually in such types that the favorable soil (capacities) for the development of various and manifold disease processes are found. It is mainly these types that fill to overflowing our penitentiaries, houses of correction, special colonies, almshouses, hospitals and offices. Human experience teaches (1) that many of such types are lacking in capacities for adaptation in general, (2) that their resistance in the broadest sense is often poor, and (3) that many of them succumb early in life and proportionately few of them attain even moderately long life.

My comparative studies of individuals, of members of families and of groups have shown that it is in those who are found to be innately more or less remote from an easily recognized ideal in total makeup and adaptation, the weak, the unhealthy, the plus-potentially unhealthy, that the scaphoid type of scapula is most frequently found, conversely, that it is in those found to be innately nearer to such an ideal, the strong, the healthy, the plus-potentially healthy of the race, that the convex type of scapula is most frequently found.

#### THE AGE INCIDENCE OF SCAPULAR TYPES TABULATIONS

Attention is next directed to the age incidence of scapular types, a finding as yet unparalleled in mammalian morphology. "That the scaphoid scapula occurs with great frequency among the young, but is relatively infrequent among the old" was a statement made by me in 1911.<sup>11</sup> I have, however, refrained from giving it that degree of emphasis, which after seventeen years of observation and research now seems to be justified. The statement was based on the observations that each scapular type discloses an age incidence, i. e., the convex increases, whereas, the straight, like the concave, decreases in frequency of occurrence with each successive age period from birth to old age when relatively large groups of individuals, representing each successive age period, are investigated. Personal investigations indicate that in the mixed white stocks represented in our population, in the first ten years of life approximately 80 per cent of such aged persons are possessors of the scaphoid, and approximately only 20 per cent are possessors of the convex, whereas in the age period between 70 and 80 years approxi-

mately only 20 per cent of such aged persons are now the possessors of the scaphoid and approximately 80 per cent of such are now the possessors of the convex

A number of independent, rather extensive investigations of similar and dissimilar material in different populations, have been made in reference to percentages of convex, straight and concave scapular types, covering the successive decenniums of life in the living and the dead. The results of some of these investigations have been published and others communicated. The figures secured by all those who had more or less understood the classification, or appreciated the age incidence, or both are arranged in Table 1.

#### COMMENT

Table 1 contains the classification of 100 fetal scapulae from approximately the tenth week to full-term gestation (I) and of 1 219 mature skeletal scapulae whose bearers were of an approximate average of 50 years (§). Twenty-one thousand two hundred and twenty-nine (21 229) observations on living, necropsy, fetal and skeletal material are included in the table, of these, 2,772 represent the dead and 18,457 the living. The material is from various sources, some of which is similar and much of which is dissimilar, and it represents the work of different investigators in classifying human scapulae in the living and the dead. Moreover, the classification of scapulae in the living by independent workers represents phases of physical examination never before attempted. Under such circumstances there are, of course, inaccuracies in the figures which are due either to unavoidable or improper technic, or to lack of complete understanding of the classification. It was not fully understood by Warburg,<sup>16</sup> hence his percentage of "scaphoid" is rather high for the age and nature of his material, nor by Kollert,<sup>24</sup> who did not sharply differentiate between the *straight* and *convex*, hence his figures for *convex* are from 15 to 35 per cent too high in the several age periods. Cunningham's<sup>15</sup> percentage of *concave*, like that of Weiss is too high for both the age period and the character of the material. Weiss (†) was forced by public school regulations to examine through the clothing. Cunningham attempted to classify scapular types by exact measurements—something obviously not possible either on living or skeletal material. Nevertheless, the percentage of straight and concave (scaphoid) when combined in the tabulation of both Cunningham and Weiss represent the approximate expectancy in percentages for the respective material and age periods. There are

24 Kollert, V. Ueber die skaphoide form des Schulterblattes, Wien klin Wchnschr **24** 1299-1301 1911. Das skaphoide Schulterblatt und seine klinische Bedeutung für Prognose der Lebensdauer. Wien klin Wchnschr **25** 2002-2006, 1912, Interstate Med J **21** 1104-1114, 1914 (translation by T. Romeiser).



TABLE 1—*The Age Incidence of Scapular Types Represented in Fetal and Postnatal Periods of Life*

Observer and Material	Age Period	Number of Persons	"Convex" per Cent	"Straight" per Cent	"Concave" per Cent	"Straight" + "Concave" = "Scaphoid" Type, %
†Graves, W W Prenatal life, male and female (white), private collection	Approx 10 wks to 9 mos incl	100	26 0	49 0	25 0	74 0
Graves, W W St Louis Health Show, male and female (white)	3 mos to 67 mos incl	422	18 0	56 0	26 0	82 0
§Graves, W W Dissecting room, male and female, (mixed stock) various sources	50 approx average	1 219	54 3	27 0	18 7	45 7
Warburg, F Cologne Public School (white), male and female	6-7 incl	1 000	12 6	62 3	25 1	87 9 (?)
†Weiss, W St Louis Public School (white), male and female	5-15 incl	5 325	18 5	29 7 (?)	51 8 (?)	81 5
Graves, W W Orphan Asylum (white), approx 30% of number retarded, male	5-14 incl	300	11 8	35 2	54 0	89 2
Graves, W W Combined St Louis Infirmary, City Hospital and Masonic Home (white), male and female	40-50	167	54 1	27 4	18 5	45 9
	50-60	174	61 6	24 1	14 3	38 4
	60-70	275	70 0	20 3	9 7	30 0
	70-80	268	81 4	12 7	5 9	18 6
	80-90+	116	88 6	8 3	3 1	12 4
Graves, W W Dissecting room, male and female (white), Department of Anatomy Western Reserve University	20-30	45	42 2	33 3	24 5	57 8
	30-40	105	53 3	26 6	20 1	46 7
	40-50	129	60 1	23 2	16 7	39 9
	50-60	88	59 1	26 1	14 8	40 9
	60-70	63	76 2	17 4	6 4	23 8
Kollert, V Neeropsies at Institute of Pathological Anatomy, Vienna, Austria, male and female	70-90	28	92 1	14 3	3 6	17 9
	0-10	368	38 6	34 5	26 9	61 4
	10-20	46	30 4	21 7	47 9	69 6
	20-30	125	53 6	25 6	20 8	46 4
	30-40	116	63 8	21 6	14 6	36 2
	40-50	123	74 8 (?)	22 1	3 1	25 2
	50-60	130	75 4	15 4	9 2	24 6
	60-70	58	72 5	22 4	5 0	27 5
	70-90	34	88 2	8 9	2 9	11 8
	20-34+	270	18 0	20 0	62 0	82 0
Ball and Thomas Prostitutes (white), California						
Cunningham, R University students California (white), male and female	16-25	1,057	28 0	15 0 (?)	57 0 (?)	72 0
†Butts, Heber U S N and M C officers and enlisted men (white) 1913	20-30+	500	67 2	14 4	18 4	32 8
†Ball, J D U S Army officers in training, 1918	20-30	976	47 6	23 2	29 2	52 4
	30-40	472	54 9	17 6	27 5	45 1
†Ball J D U S Army returned overseas men, 1919	20-30	2,738	49 5	37 3	13 2	50 5
	30-40	779	67 3	24 6	8 1	32 7
†Weaver A C U S Army hospitalized men St Louis	20-33 incl	939	46 2	18 6	35 2	53 8
†Mackey, D E Traumatized from X ray plates, U S Army hospitalized men Army Medical School	18-30 incl	1,000	40 6	35 6	23 8	59 4
†Krause, I B, and Howard S P Missouri State Prison (white), male*	20-40	381	21 0	45 4	33 6	79 0
	40-72	59	30 7	37 7	31 6	69 3
†Staff of Fulton, Missouri, State Hospital for Insane, male and female (white)	20-29	103	19+	47+	33+	80+
	30-39	201	33+	42+	23+	65+
	40-49	326	34+	44+	21+	65+
	50-59	266	39+	45+	15+	60+
	60-69	197	45+	41+	13+	54+
	70 and over	131	49+	35+	15+	50+

\* Included in the period 20-40 years are 43 persons under 20 as follows 1 at 16, 6 at 17 14 at 18, and 22 at 19 years In the period 30-72 years 85 persons are between 30 and 40, 42 between 40 and 50 9 between 50 and 60, and 8 between 60 and 72 The tabulation represents the first returns from a survey of the entire prison population, numbering approximately 2 500 persons

† Personal communications

‡ The collection consists at this time of approximately 400 specimens and the tabulation represents the result of the first hundred examined The sources of the collection were both local and general but mainly general, in response to an appeal for fetal material published in the J A M A<sup>21</sup> and other American journals in 1919

§ The average age of dissecting room material was approximated (1) from data on 1 009 bodies supplied by Dr Ales Hrdlicka and acquired by him in the Anatomical Department, Columbia University (Prof George S Huntington) and (2) from data supplied by Dr D M Shoemaker St Louis, on 750 bodies distributed to the medical schools of Missouri, in a recent three year period The range in years of the Missouri material was from 28 to 92 the average age 54 6 years and that from Columbia University from 15 to 96 average age from 46 8 years Represented in the tabulation are 198 bones classified in the Departments of Anatomy St Louis University School of Medicine and Washington University Medical School, 150 bones in the Department of Anatomy University of Berlin, 602 bones in the Wistar Institute of Anatomy and Biology, and 269 bones in the United States National Museum (Huntington collection) total 1,219 bones with approximate average age of bearers of 50 years The following table, recently compiled by Prof T Wingate Todd, Western Reserve University here published with his permission gives the first exact information on minimum, maximum and average age of white and negro male and white and negro female dissecting room material

	Number of Skeletons	Minimum	Maximum	Average
Male white	564	18	88	48 9
Female white	74	16	80	42 8
Male negro	178	17	70	35 7
Female negro	44	16	87	38 7
Total	860	16	88	43 6

doubtless other inaccuracies in the tabulations, including my own. By establishing uniform methods in recognizing, recording and tabulating scapular types, as suggested in the concluding paragraphs of this communication, avoidable or improper methods leading to inaccuracies should be reduced to a minimum in future work.

The personal equation, however accurate one may be in any endeavor, is a factor that must always be considered. This equation is doubtless represented in the results of every investigation tabulated above. Notwithstanding the personal equation, the inaccuracies in the table and the lack of uniformity in the material, the figures from different sources representing similar material show striking similarities. The age incidence of each scapular type is shown by the percentages found in practically any two successive age periods in the tabulation of Ball, Kollert and myself. Careful consideration of Table 1 makes it apparent that there is a gradual decrease in the percentage of scaphoids (straight and concave), and a gradual increase in percentage of the convex in successive decenniums. This fact supplies an additional biologic reason for combining the *straight* and *concave* into a single type, namely, the *scaphoid*. Moreover, the figures justify authors of textbooks in describing and picturing the scapular vertebral border as more or less convex, because the figures show that the convex is still the predominating type in living and anatomic material in our population after the fifth decennium of life, which decennium represents the average age of anatomic material.

Having pointed out the nature of, and the lack of uniformity in, the material and the reasons for the inaccuracies in the investigations, attention is now directed to some of the studies bearing on the possible significance of the age incidence of scapular types. (1) To the unusually large percentage of the scaphoid type in German public school children, aged from 6 to 7 years (Warburg<sup>16</sup>), and also to the approximately correct percentage of this type in St. Louis public school children, aged from 5 to 14 years (Weiss †), (2) to the relatively large percentage of the scaphoids in university students, aged from 16 to 25 (Cunningham<sup>15</sup>), and to the contrast of the figures in that study with those on prostitutes, aged from 20 to 34 years, in the same territory, giving a larger percentage of scaphoids even at a greater age period (Ball and Thomas<sup>25</sup>), (3) to the splendid investigations of Ball (†) on officers in training and returned overseas men, and (4) to those of Butts (†) on U. S. Navy and Marine Corps officers and men, of Weaver (†) on hospitalized overseas men and of Mackey (†) on roentgen-ray plates on U. S. ex-service men. The groups found in the work of Ball, Butts, Weaver and Mackey have

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25 Ball, J. D., and Thomas, H. G. A Sociological, Neurological, Serological and Psychiatric Study of a Group of Prostitutes, *Am. J. Insan.* **74**: 647-666, 1917-1918.

this in common that they represent the most rigid selection by physical and mental tests of the army and navy. Weaver's and Mackey's groups of ex-service hospitalized men show somewhat larger percentages of scaphoids than do the groups of Ball and Butts for approximately the same age periods. In this connection, the army, navy and university groups lend themselves to comparison with the prostitute group and with the prison group (Krause and Howard, and with Fulton, Missouri State Hospital group †). Special attention is called to the remarkable group of Kollert, representing 1,000 necropsies from before birth to old age. Finally, attention is called to (a) the more rapid decrease of the *concave* than the *straight* in successive age periods (b) to the more rapid *decrease* in the straight and concave, conversely, to the more rapid *increase* in the convex after than before the maturity of the human scapula (from the 20th to 25th year of life). No further comment, at this place, seems necessary other than that the figures are meager, indeed, when compared with their possible significance. They show beyond all cavil or doubt just what they are intended to show, that each scapular type has an age incidence. The figures establish that fact, but they do not and cannot explain it. Its explanation is an important problem in connection with human morphogenesis.

#### THE PROBLEM TWO POSSIBLE EXPLANATIONS

The relative frequency of convex and scaphoid types in all periods of life, and striking difference in their percentages in the extremes of life postulate two possible explanations of the age incidence. First the scaphoid is changed into the convex in most individuals during the course of years. Second, the scaphoid is not changed into the convex during the course of years. If ample evidence can be found in support of the first explanation, we shall then establish a finding heretofore unrecognized in mammalian ontogenesis, on the other hand, if we can find ample evidence in support of the second explanation, we shall then establish some relation of the age incidence of the types of one morphologic feature (the scapula) to longevity, and if to longevity, to morbidity and adaptability in general. From the very outset of my investigations, it was obvious that change of one type into another implied natural processes of bone growth, or modification of natural processes by muscle influence (variation, pull), or by disease, or by environmental influence. Moreover, it was obvious that natural processes, whether modified or not, become operative very early in prenatal life and persist throughout development into maturity and senescence. The problem from the beginning has been and is. What is the tenable explanation of the age incidence? This problem has been approached from various angles, but space forbids more than mentioning the scope of investigations and some of the results with brief comment on them.

## SCOPE OF INVESTIGATIONS

(1) Comparative anatomy of scapulae and of other bones, and consideration of the literature on this subject and on normal bone growth and its possible modification by environmental influences from birth to old age, (2) morphology of human scapulae in prenatal and postnatal growth periods to maturity (25th year of life) and onward,<sup>11</sup> (3) morphology of scapulae in several lower mammalian families during prenatal and postnatal life periods, (4) variations of muscles and their attachments in relation to scapular types in fetal and postnatal periods of human life, (5) age changes of human and other mammalian scapulae from birth to maturity and from maturity to old age,<sup>11</sup> (6) racial occurrence and distribution of scapular types in ancient and modern man,<sup>11</sup> (7) relation of scapular types to sex, race, stock, type, build and of modifying influences on scapular types of environment, including occupation, social level, health, disease (rickets, endocrine disturbances, paralysis) amputations, etc., (8) heretofore, recognized anatomic, physiologic, mental and moral inherited variations coexistent with each scapular type,<sup>11</sup> (9) possible modifying influence on the degrees of convexity and concavity of scapular types by right or left handedness, (10) scapular type (vertebral border) symmetry and asymmetry from the tenth fetal week onward throughout postnatal life periods, (11) comparative studies of detached individuals, of individuals of families and of so-called "normal" and "abnormal" groups, (12) follow-up observations on a number of individuals, representing successive age periods in reference to the possibility of change of one type into another both during growth periods and after maturity<sup>11</sup>

## RESULTS

Some of the results of the foregoing investigations have already been briefly summarized in this paper, some are published, some are still unpublished, and none is complete

1 At approximately ten weeks in development the human scapula has attained the general form and particular type which it apparently ever afterward retains and, with but few exceptions, it becomes completely ossified (mature bone) between the 20th and 25th year of life. Even prior to the tenth fetal week, reconstructed serial sections of the shoulder girdle (Hagen,<sup>26</sup> Bardeen and Lewis<sup>27</sup> and Lewis<sup>28</sup>) have revealed the presence of convex and concave types

26 Hagen, W. Die Bildung des Knorpelskelets beim menschlichen Embryo, *Arch f Anat u Entwicklungs geschichte*, 1900, p 1

27 Bardeen, C. R., and Lewis, W. H. Development of the Limbs, Body Wall and Back in Man, *Am J Anat* 11, 1901-1902

28 Lewis, W. H. Development of the Arm in Man, *Ibid*, p 145

2 Change of the scaphoid into the convex at any time after type formation and during subsequent life periods implies not merely an alteration in vertebral border contour but a reconstruction or remodeling of the entire bone, an event wholly unparalleled in bone growth and one wholly without precedent in the human skeleton incident to any natural process as yet known

3 The analogies of skull forms, and the form or character of other discernible inherited morphologic features, show that the types of such features remain more or less fixed throughout the subsequent life of the individual from early life to maturity and onward. It is, therefore, wholly improbable that the human scapula could be the only discernible morphologic feature whose types are completely changed from one into another both during and after the developmental periods of life

4 Particular variations of scapular muscles or of their attachments have not been found to be associated exclusively with any particular scapular type in any period of life, either in my dissections or in those of others. Such variations cannot be interpreted as causes of scapular types as recently inferred by Balli,<sup>20</sup> rather are they to be interpreted as associated variations. Inherited variations of bones, muscles and of morphologic features generally have heretofore been considered expressions of the anlage peculiar to the individual in which they are found. The influence of muscles, or of their attachments, or of muscle variations, or of muscle pull, either on scapular type formation, alteration or modification must be considered negligible when we remember that as early as the tenth fetal week each scapular type is found

5 Convex, straight and concave types are found in all postnatal life periods in varying degrees and percentages in the tall, the short, the fat, the lean, the broad backs, the narrow backs, the weak, the strong, the healthy, the sick, the near to and the remote from, the ideal in development, the mentally brilliant, average and defective, the well and poorly muscled, the "excellent," "good" and "poor" types, regardless of race, stock, sex, social level, occupation or environment

6 Scapular type symmetries and asymmetries (comparing one vertebral border with the other) are found in both prenatal and postnatal life periods from the tenth fetal week onward. Occasionally one finds an individual with convex on one side and concave on the other, and a rather frequent finding is straight on one side and concave on the other. Similar scapular type symmetries and asymmetries are found in immature and mature mammalian scapulae (orang-utan, gorilla, chimpanzee, flying lemur, bat, armadillo, hedgehog, etc.). The presence of all such scapular type asymmetries both in prenatal and postnatal life periods show them to be independent of right or left handedness, independent of occupation and other environmental influences

Usually similar, but occasionally dissimilar, types are found in twins both in prenatal and postnatal life periods. Draeseke<sup>14</sup> reports male twins one of which has convex scapulae, the other concave scapulae.

7 The finding of similar scapular types in ancient and modern man, their racial distribution, their hereditary nature and the finding of similar types in some lower mammals leave but little foundation for the assumption that the human scapula, by any natural process as yet known, becomes changed in type at any time after its earliest type formation.

8 The increase in the percentages of the convex and the decrease in the percentages of the scaphoid (occurring more rapidly after than before maturity), lead to the reasonable conclusion that neither natural processes of bone growth or their modifications change the scaphoid into the convex either before or after maturity of the bone. Not only do the figures in Table 1 justify this conclusion, but every investigation thus far undertaken justifies it.

9 Realizing that final and complete explanation of the age incidence depended on follow-up observations on a number of individuals from birth to maturity and onward, I began such observations on approximately 200 individuals, representing successive age periods, in 1907. Thus far scapular types have remained fixed not only during life periods after maturity but also during periods of growth and development.

Considering the scope and results of investigations herein outlined, it appears that one type of scapula is not changed into another at any time during a person's development and life.

#### THE USEFULNESS OF SCAPULAR TYPES

The usefulness of scapular types is firmly grounded in their relations to problems of heredity and longevity. Obviously, if they do not change, our figures indicate decreased mortality in many of those possessing the convex and increased mortality in many of those possessing the scaphoid. Our figures, however, express the results of observations on the inherited types of only one part of man's makeup, hence they are for this and other obvious reasons neither similar, nor are they comparable, to those of life and mortality tables. Nevertheless, they bring unmistakable evidence in support of a variable relation of heredity to longevity, a relation long recognized by physicians, biologists and biometricians. A recent mathematical discussion by Pearl<sup>29</sup> "Indicates that from one-half to three-fourths of the death rate is selective in character, because that proportion is determined by hereditary factors. Just in proportion as heredity determines the death rate, so is the mortality selective."

29 Pearl, Raymond. *The Biology of Death*, p. 177, J. B. Lippincott Co., 1922.

I here merely suggest that scapular types may serve as useful aids in recognizing those hereditary factors on which a portion of "selective" mortality and morbidity depend

The relations of scapular types to problems of heredity and longevity, and the contrast between scapular type percentages of dissimilar material for similar age periods (Table 1) justifies the inference of inherent strength (good adaptations) and decreased morbidity in many of those possessing the convex, conversely, the inference of inherent

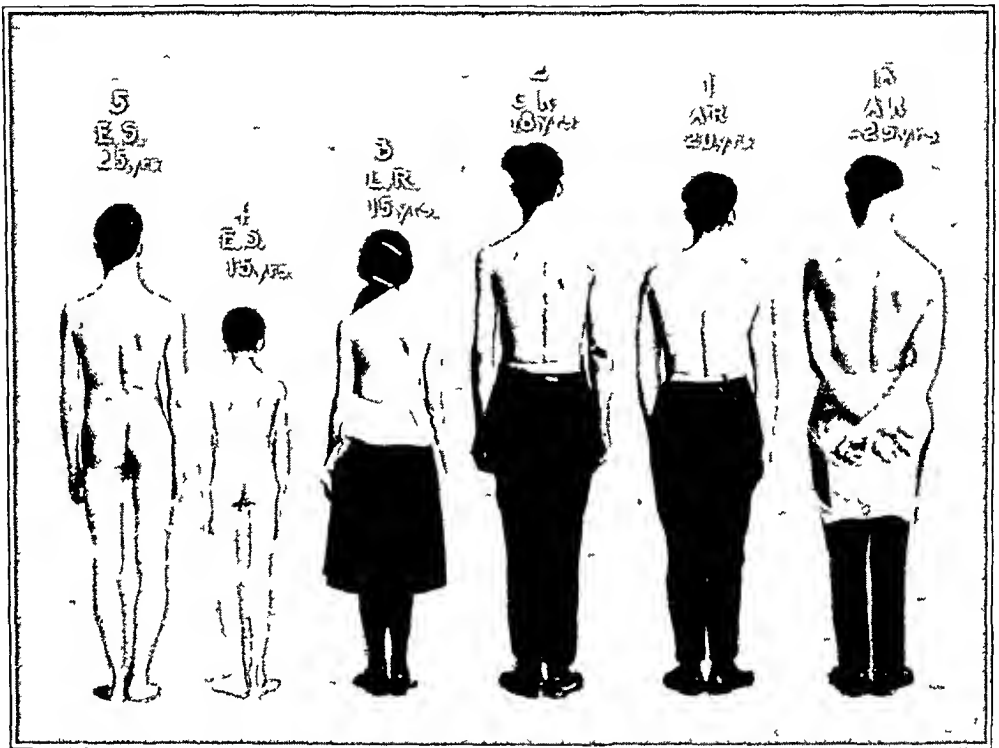


Fig 4—Scapular types, after several years growth in the progeny of the R1 family and in E S, a member of the S12 family Compare Figures 1, 2, 3 and 1A with those of the same persons shown in Figure 1 Figures 4 and 5 represent E S at 15 and 25 years of age

weakness (poor adaptations) and increased morbidity in many of those possessing the scaphoid

We have long known that all human beings are susceptible to disease some more, some less The questions are therefore pertinent, who among us in the broadest sense, are the more susceptible? Who are the more immune? We do not yet study the apparently healthy persons as intensively as we study the definitely sick We do not yet investigate all the discernible inborn factors underlying health or disease Just so long as we fail to search for the innate differences in persons, we shall fail to

appreciate the soil factors, or capacities, underlying health or disease and shall fall short of the possibilities in disease recognition, prevention and cure

The investigations of Kollert,<sup>24</sup> Reye,<sup>13</sup> Nonne,<sup>30</sup> Thielke,<sup>19</sup> Draeseke,<sup>14</sup> Chotzen,<sup>31</sup> Kellner,<sup>32</sup> Clemens,<sup>33</sup> Ball and Thomas,<sup>25</sup> Mackey † and Hosteing,<sup>18</sup> as well as my own,<sup>11</sup> have shown that the scaphoid type of scapula is more frequently coexistent than is the convex, with a basic pathology, with an inborn unduly disease susceptible soil

#### SUMMARY AND CONCLUSIONS

1 Observations on the R 1 family, in 1906, led me to classify human scapulae into convex, straight and concave types and to designate both the straight and concave the scaphoid

2 Investigations of living, fetal and skeletal (ancient and modern) material and of lower mammalian material revealed the hereditary nature, primal origin, of each scapular type

3 Comparative clinical and anthropometric studies of members of families through as many generations as possible showed that scapular type inheritance is usually dependent on scapular type matings, and that disease and possibly other poison factors may occasionally "alter" such inheritance

4 Investigations of comparable groups, representing living, necropsy and skeletal material of known age disclosed a finding as yet unparalleled in mammalian morphology the age incidence of scapular types, i e., the convex increases while the straight and concave decrease in frequency of occurrence in successive age periods from birth to old age

5 The age incidence required explanation, hence investigations were inaugurated to determine whether one scapular type changes into another The results of the investigations justify the conclusions (1) that no natural process or circumstance as yet known changes the scaphoid into the convex after earliest type formation (approximately tenth fetal week), and (2) that the scaphoid is more often found than is the convex in the plus-potentially sick, the shorter-lived of the race

6 While our investigations are in no particular complete, nevertheless the results thus far secured clearly show the usefulness of scapular types in studies of human heredity, longevity, morbidity and adaptability in general Scapular types, however, are not standards with which we

30 Nonne, M Scapula scaphoidea (Graves), *Deutsch med Wchnschr* **43** 159, 1917

31 Chotzen, F Ueber vorkommen Bedeutung der Scapula scaphoidea, *Berl klin Wchnschr* **55** 949, 1918

32 Kellner Scapulae Scaphoidea, *Deutsch med Wchnschr* **37** 94, 1911

33 Clemens, D Syphilis u Schwachsinn, *Ztschr f d Exforsch u Behandl d Tugendliche Schwachsinn* **6** 353-357, 1912

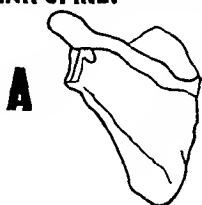


may measure man, any of his structures or any of his functions. A particular scapular type is only one part of an individual's inheritance, hence it is a conditional, not an absolute index of constitution.

7 The finding of the age incidence of scapular types disclosed the heretofore unrecognized principle of investigating inherited variations, whether of structure or function, in successive age periods from early life to old age. Further application of this principle gives promise of finding other age incidences of similar import.

## SCAPULAR CLASSIFICATION CONVEX-STRAIGHT-CONCAVE

BASED PRIMARILY ON CHARACTER OF GREATER PORTION OF VERTEBRAL-BORDER CONTOUR BELOW SCAPULAR SPINE.



**A**

THE **CONVEX** TYPE: MAY BE REGULARLY OR IRREGULARLY SLIGHTLY-Cv1, MODERATELY-Cv2, OR MARKEDLY-Cv3 CONVEX.

**B**



THE **STRAIGHT** TYPE: STRAIGHT OR NEARLY SO, NEITHER CONVEX NOR CONCAVE, TENDING RATHER TO CONCAVITY THAN TO CONVEXITY.

**C**



THE **CONCAVE** TYPE: MAY BE REGULARLY OR IRREGULARLY, SLIGHTLY Cc1, MODERATELY-Cc2, OR MARKEDLY-Cc3 CONCAVE.

THE **SCAPHOID** TYPE COMBINES 12 OR MORE ANATOMICAL AND ARCHITECTURAL FEATURES COMMON TO STRAIGHT AND CONCAVE WHICH CONTRAST VIVIDLY WITH SIMILAR FEATURES IN THE CONVEX.

GRAVES AM J PHYS ANTHRO  
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Fig 5—Outline drawings, by P. A. Conrath. A—Convex “Cv2” type, B—Straight “St” (scaphoid) type, and C—Concave “Cc3” (scaphoid) type.

### POSSIBILITIES OF FURTHER RESEARCH

Since human beings differ in their innate capacities for adaptation, inherited variations represent vital and practical problems of biology and clinical medicine, meriting general research in the following directions: (a) Further use of ascendants and collaterals as biologic standards in comparative anthropometric and clinical studies of families, through as many generations as possible, in reference to “normal” and “altered”

inheritance of scapular types and of other variations, (b) Accumulation of additional data on the age incidence of scapular types in so-called "normal" and "abnormal" groups of living, necropsy and skeletal material of known age in successive age periods, (c) More information bearing on the explanation of the age incidence as may be secured from further follow-up observations, and (d) Further investigation of the relations of scapular types and other inherited variations to problems of heredity, longevity, morbidity and adaptability in general. These lines of endeavor may lead to a fuller appreciation of individual constitution and to a clearer recognition of the factors of heredity and environment underlying health and disease, racial betterment and racial deterioration.

#### METHODS OF RECOGNIZING, RECORDING AND TABULATING SCAPULAR TYPES

Remembering the classification described and pictured in Figure 5, one will seldom find a scapula in the living subject that cannot be readily classified by inspection and palpation, except in obese individuals, and in such the roentgen ray may be employed.<sup>11</sup> In order that the personal equation and avoidable inaccuracies in scapular classification on the living may be minimized the following methods and precautions are suggested.

*Inspection* —While the subject is stripped, at least to the waist line, and standing at ease in a good light, one should note general development and attitudes, topography of trunk, form of chest, course of clavicles, right and left acromial level, squared, drooped or rounded shoulders, spinal curves, length of neck and the relation of scapular vertebral borders to vertebral axis. The modeling of these borders below the scapular spine may be seen in most persons. Regardless of type the vertebral border may be prominent, wing-like (*scapula alata*). The dimensions and form of the interscapular space below the scapular spine are dependable signs of type. It is often narrowed in the convex, widened in the straight and concave. Usually in the convex, the form of this space is roughly A-shaped, the general direction of the vertebral border is downward and outward, the inferior angle of each bone is from 1 to 4 cm. further away from the vertebral axis than is the base of the scapular spine. As a rule, in the straight or concave the base of the scapular spine and the inferior angle are equidistant, or nearly so, from the vertebral axis, the form of the interscapular space is roughly H-shaped, but in some instances it is roughly V-shaped. The general direction of each vertebral border is downward and inward.

*Palpation* —Asymmetries in type (mixed types) and differences in degree of convexity or concavity render it necessary to palpate the

contour of each vertebral border In mixed types one occasionally finds convex + concave, more frequently convex + straight and still more frequently straight + concave One may bring out the contour of each vertebral border by several methods, but the following have been found to be reliable (1) If the examiner is right-handed, he should face and stand close to the left side of the subject, place his left hand over upper portion of the subject's right arm and bring rather firm pressure to bear between his own left arm and chest on the subject's shoulder-girdle regions (2) The examiner flexes the subject's pronated forearms and places them over the small of the back One may combine both methods and thus secure a control

The prime purpose of either or any method is to bring about greater relaxation of rhomboid and trapezius muscles, and to elevate the vertebral borders from the chest wall With this accomplished, one may now more readily see their modeling, palpate and compare them Palpation should be made at a right angle or nearly so with the contour of the vertebral border, slowly and firmly without pain or discomfort to the subject Undue haste or force defeats the purpose by exciting muscle contraction and resistance The classification, as well as the degree of convexity or concavity, should now be determined During palpation the examiner should neither see nor feel contractions of shoulder-girdle muscles, and especially in the rhomboid and trapezius If contractions in these muscles are seen or felt, the findings may be faulty, for example, a straight or moderately concave may be called a convex

*Roentgen-Ray Examination*—Except in the obese, this method is less reliable than combined inspection and palpation because of possible shadow distortion In age periods prior to 16 years in living subjects, it is likely to be unreliable, because the vertebral border and the inferior angle regions are still partly cartilage, and the cartilage is but dimly, if at all, shown by the roentgen ray In such examination the subject should rest with the back on a plate, with the arms resting close to the sides and forearms in a position of moderate supination In this position one will secure the least distortion of vertebral border shadows

*Recording*—Because "mixed types" occur, the record should show classification of each scapula If the greater part of the vertebral border between base of scapular spine and inferior angle region is found to be convex, depending on the degree of convexity, it is recorded Cv1, Cv2 or Cv3 If the greater part of this portion of the border is found to be straight, it is recorded St, and if concave, depending on the degree of concavity, it is recorded Cc1, Cc2 or Cc3 One should always keep a record of those individuals whose scapulae cannot be classified and give reason obese, resistant or anatomic

*Tabulation*—In tabulating the results of classification in each age period, one should arrange columns headed age period, convex, straight, concave and other columns headed convex + straight, convex + concave, straight + concave, not classified. A tabular form for the age period from 10 to 19 years, representing scapular classification of 500 persons let us assume to be as follows

TABLE 2—*Age Period, Representing Scapular Classification of Five Hundred Persons*

Age Period	Convex		Straight		Concave		Convex + Straight		Convex + Concave		Straight + Concave		Not Classified		Total	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
10 to	110	= 22	190	= 38	100	= 20	25	= 5	5	= 1	60	= 12	10	= 2	500	100
	12 5		12 5		2 5		25		5		60					
19 yrs	2 5		30		30		—	=	—	=	—	=				
							2		2		2					
							(12 5 Cv)		(2 5 Cv)		(30 St)					
							(12 5 St)		(2 5 Cc)		(30 Cc)					
	125		232 5		132 5								10		500	
	25%		46 5%		26 5%								2%			100%
							Mixed types	25	+	5	+	60	= 90			
								5%	+	1%	+	12%	= 18%			

The percentages in the columns headed convex, straight or concave in the group of 500 are readily calculated. The results, however, would not represent the percentages of all types in the entire group, because the "mixed" types have not yet been divided and apportioned. The total number of persons in each mixed type column should now be divided equally and one-half of the number apportioned to each column represented in a given "mixed type." For example, we find twenty-five individuals in the column headed "convex + straight", 12 5 of this number is now added to the column headed "convex" and 12 5 to the column headed "straight." We find in the column headed "convex + concave" five individuals, and similarly dividing this number we add 2 5 to the column headed "convex" and 2 5 to the column headed "concave." Similarly dividing and apportioning the number found in the "straight + concave" column gives the total scapular classification expressed in numbers and percentages as above. One should also figure and tabulate (as above) the percentages of the "mixed-type" and of the "not-classified" columns in each age period for comparison with other age periods, other material and with the tabulations of other examiners.

*Data for Correlation*—In the study of persons singly or in groups, the following data are indispensable: age, sex, race or stock, occupation, social condition, mental level, weight, standing height and in the sick the clinical diagnosis. Much to be desired additional data for correlation are sitting height, anteroposterior and transverse skull and chest measurements, associated asymmetries, disproportions, disharmonies of

structures and functions, including those discernible variations usually called stigmas For a summary of so-called stigmas see the article of Walton <sup>34</sup> For all anthropometric measurements the methods given by Hrdlička <sup>35</sup> are recommended

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34 Walton, G L See Posey and Spiller, *The Eye and the Nervous System*, Philadelphia, J B Lippincott Company, 1906, pp 950-971

35 Hrdlička, A *Anthropometry*, Philadelphia, Wistar Institute of Biology and Anatomy, 1920

# PRIMARY SARCOMA OF THE STOMACH \*

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NEW YORK

That primary sarcoma of the stomach is rare has been recognized by our pathologists. Several writers have collected reports of these tumors. In 1900, Fenwick<sup>1</sup> collected sixty cases in the literature and concluded that fifty-three were authentic. Flebbe,<sup>2</sup> in 1914, collected 157 cases. Haggard<sup>3</sup> collected 244 cases in 1920.

The rarity of these tumors is readily seen from this list. One sarcoma of stomach in 840 specimens (Berlin Pathological Institute), six in 13,387 necropsies (Hirsch), and eight in 2,069 malignancies of stomach (Mayo clinic during five years).

Ewing<sup>4</sup> has stated that sarcoma of the stomach constitutes 1 per cent of gastric tumors.

The following case came under my observation while in charge of the first medical division pathological department of Columbia University at Bellevue Hospital.

## REPORT OF CASE

G D, a man, aged 77, Roumanian, single, was admitted to hospital Jan 12, 1923, with a history of weakness for the last three months. He had had gonorrhea and syphilis (fifty years ago), pneumonia and furunculosis (two years ago). There was no history of any injury. His father and mother had died of "old age." One brother was living and well and another had died of heart trouble. There was no history of any chronic disease in the family, or tobacco or alcohol.

Three months previous to admittance the patient became unconscious in the street. The onset was sudden, with weakness. There was no paralysis or injury. He was taken home and became conscious, with the intense weakness continuing. His appetite had been poor for three months, although there was no distaste for food. There was no vomiting, headaches or abdominal pain. There was burning in the epigastrium of four months' duration, with difficulty in swallowing. The patient had been losing considerable weight for several years. He occasionally had a productive cough. The bowels were constipated. There was no pain. He rose once during the night to urinate, otherwise his sleep was fair. His vision was poor and the left eye was blind. He had weighed 220 pounds (99 kg) and now weighed 175 pounds (79 kg). The loss had been rapid.

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\* From the Department of Physiology, Columbia University.

1 Fenwick. Primary Sarcoma of the Stomach, *Lancet* **1** 463 (Jan) 1901.

2 Flebbe. Ueber das Magensarkom, *Ztschr f exper Path u Therap* **12** 311-336, 1913.

3 Haggard, W D. Sarcoma of the Stomach, *Surg, Gynec & Obst* **31** 505 (Nov) 1920.

4 Ewing, James. Neoplastic Diseases, Philadelphia, W B Saunders Company, 1919.

At the time of examination the patient was lying quietly in bed and looked chronically ill. The conjunctivae were slightly injected, and there was a cataract of the left eye and arcus senilis. Several teeth were missing, several had been filled and the remainder were carious with slight pyorrhea beginning. The tongue was dry and coated, protruding in the midline. There were no abnormal masses or pulsations in the neck. The chest was symmetrical but hyperresonant throughout. The pulse was small and regular with sclerotic vessels. The heart was enlarged to the left and the sounds were poor in quality. The abdomen was slightly retracted and a mass was felt in the epigastrium. The liver was palpable, three finger breadths below the costal margin. The skin was dry and atrophic and there was moderate adenopathy. There were slight petechial edema of both legs. The blood pressure, taken on the right arm, was systolic 105, diastolic 65. The urine was acid with no albumin and a specific gravity of .020. The stool was black and gave a positive guaiac reaction. The red cell count was 2,800,000, the white cell count was 16,000 and the hemoglobin was 45 per cent. The nonprotein nitrogen in the blood was 48 mg, the creatinin



Fig 1—The stomach, showing the sarcoma in the cardiac region

1.8 mg, and the uric acid 2.26 mg. The patient died Jan 16, 1923. The diagnosis was as follows: neoplasm of the stomach, arteriosclerosis (general), chronic myocarditis, senility.

*Necropsy*—The body was that of a well developed white man, about 78 years of age, 5 feet 9 inches (164 cm) in height. The skin was much wrinkled. The hair distribution was normal. There were no noticeable changes in the external nares, mouth, ears or eyes. The external genitalia were normal.

*Abdomen*—A midline incision was made in the trunk in front. The peritoneum was smooth and glistening. The diaphragm extended upward to the fifth interspace on the right, and to the upper margin of the sixth rib on the left.

*Chest*—There was considerable yellow fat over the pericardium. The pleural cavities were dry. The lungs were normally free.

*Heart*—The visceral and parietal layers of the pericardium were smooth and glistening, and contained the normal amount of straw colored fluid. The heart was normal in size. In the right side of the heart there was a small quantity of deep red, partially clotted and fluid blood. The auriculoventricular junction admitted the entrance of two fingers. The endocardium of the right side of the heart was well preserved and the pulmonary valves and pulmonary artery were normal. The endocardium of the left side of the heart was normal. The mitral

valve was unchanged. The aortic valves were slightly thickened. The surfaces made by sectioning the heart muscle were dark red.

*Lungs*—These were easily removed. They were large of normal weight and they crepitated throughout. On the surface of both lungs there were mottled white and black regions. These black regions were more marked at the apices. The surfaces made by sectioning had a few white nodules the size of a pinhead firm and extended slightly over these surfaces. The mucosa of the large bronchi was normal. The peribronchial lymph glands were not enlarged.



Fig 2—The liver with the metastatic nodules of the sarcoma

*Spleen*—There was no noteworthy gross pathologic change.

*Pancreas*—It was small and pink. The surfaces made by sectioning were normal.

*Suprarenals*—They were small. The cortices were narrow and yellow. The medullae were smooth and gray.

*Kidneys*—They were small and embedded in fat. Their capsules were thickened and stripped with difficulty leaving a granular surface. They did not cut easily. The cortices and medullae were not well differentiated and the cortices were contracted. The pelvis contained a small amount of fat.

*Urinary Bladder*—It was slightly distended with amber colored urine. The mucosa was pale. The openings of the ureters were patent.



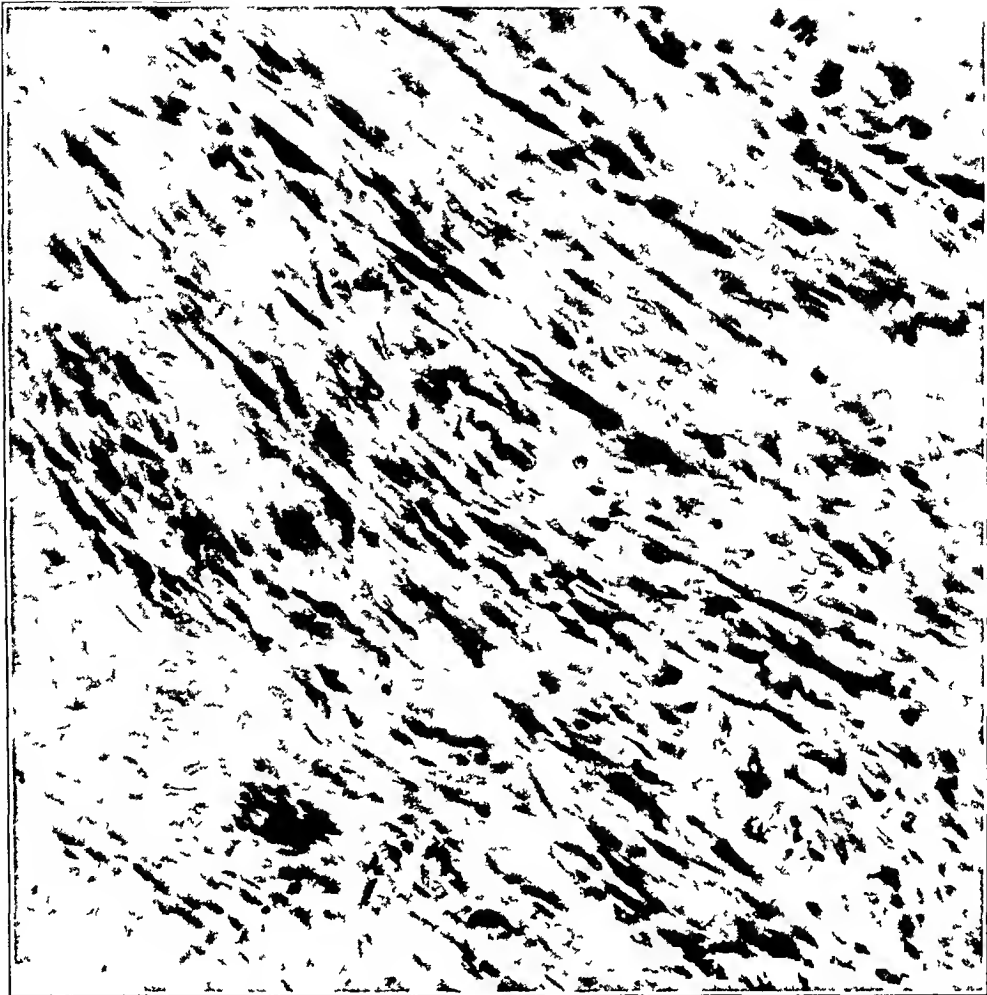


Fig 3—Microscopic section of the large spindle cell sarcoma of the stomach

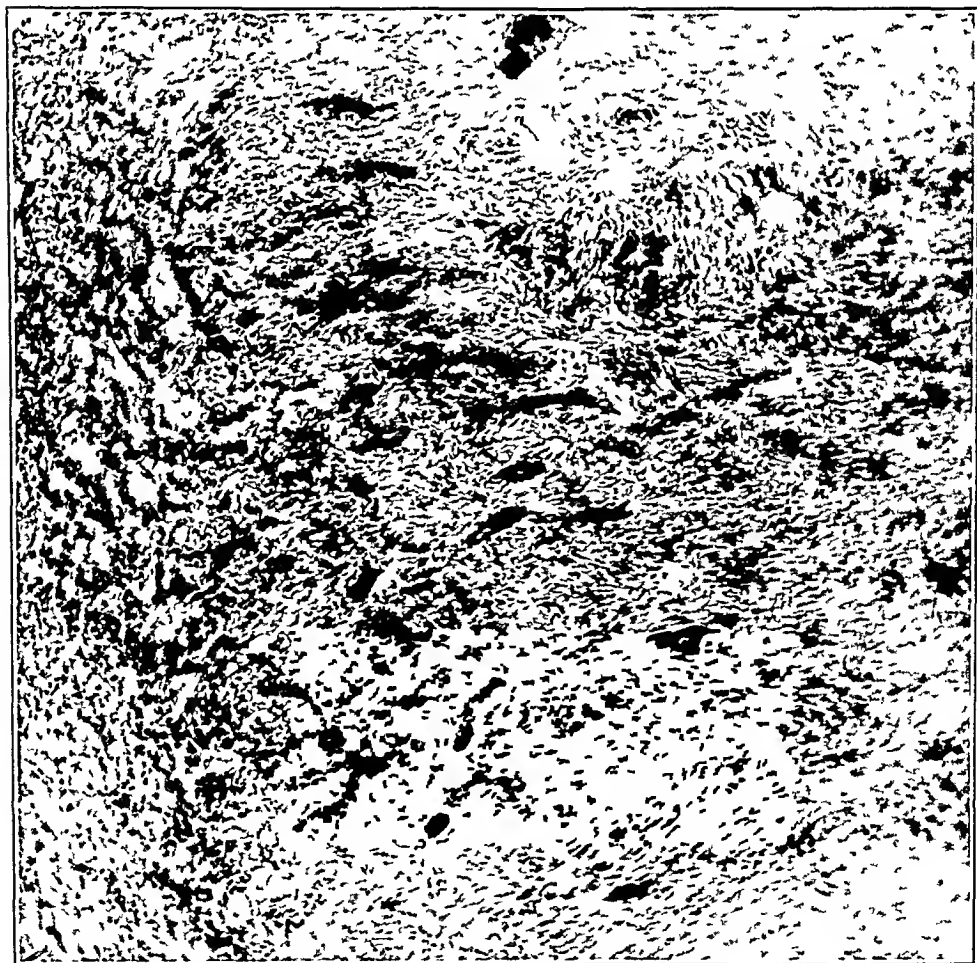


Fig 4—Microscopic section of the spindle cell sarcoma of the liver Note islands of pyknotic liver cells intermingled with the tumor cells

*Prostatic Gland*—There was no marked gross pathologic change

*Testicles*—They were small The surfaces made by sectioning were smooth and yellow The tubules were easily removed

*Aorta*—The abdominal and thoracic aortae were normal in caliber and thickness There were a few small yellow plaques about from 2 to 4 mm in diameter in the abdominal aorta

*Lymph Nodes*—The retroperitoneal lymph nodes were unchanged The organs of the neck and brain were not examined

*Stomach*—The tumor was located at the cardiac portion and was 13 cm wide and 10.3 cm long It was 5 cm thick near the center firm hard grayish white and cut with resistance Most of the tumor mass was along the greater curvature The center of the tumor was markedly ulcerated soft and irregular The surfaces made by sectioning had a fibrous appearance The outer surface of the stomach in the region of the tumor was the size of an ostrich egg and was markedly adherent to the diaphragmatic surface The stomach weighed 1680 gm It was larger than normal From the lower edge of the tumor to the pylorus it was 18.2 cm long and averaged 8.5 cm wide The rugae were distinct and the surfaces were mammillated

*Liver*—It weighed 1055 gm and was studded with huge nodules the largest measuring 2 by 1.8 cm in its largest diameter and the smallest 1 by 2 mm These nodules were umbilicated grayish yellow hard and cut with resistance On the surfaces made by sectioning there were a few small transparent regions surrounded by darker yellow zones The centers were often necrotic These surfaces were grayish yellow and had a fibrous-like arrangement of the tissue The lower surface of the inferior lobe was not so greatly involved as the upper portion but the surfaces made by sectioning had as much involvement

*Anatomic Diagnosis*—Primary neoplasm of the cardiac portion of the stomach metastatic neoplasm of the liver chronic interstitial nephritis, emphysema of the lungs general arteriosclerosis

*Microscopic Pathology*—The cells in the tumor were arranged in bundles and had replaced the normal tissue The bundles and cells were closely packed together The cells were spindle shaped and the majority were large hyperchromatic and irregular The nuclei contained much chromatin and there were nucleoli in 80 per cent of the cells

*Liver*—The nodules contained cells closely resembling those described in the foregoing paragraph Normal liver tissue surrounded these nodules but the liver cells immediately surrounding the tumors were pyknotic and loosely arranged On the outer edge of the nodules were islands of pyknotic liver cells

*Microscopic Diagnosis*—Large spindle-cell sarcoma of the stomach, with metastatic sarcoma of the liver

# CALCIFICATION OF THE HEART ITS ROENTGENOLOGIC DEMONSTRATION

REVIEW OF LITERATURE AND THEORIES ON MYOCARDIAL  
CALCIFICATION \*

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NEW YORK

The case presented herewith is the first one on record in which calcification of the heart muscle itself, without involvement of the pericardium, has been demonstrated radiographically *intra vitam*, and in which the roentgen-ray diagnosis was confirmed by necropsy. The finding was detected accidentally, in the course of a special type of roentgenologic investigations carried on for several years at the Montefiore Home and Hospital. After two years of comparative radiographic and gross pathologic studies on a large scale it was found that quite often pathologic conditions which could have been diagnosed roentgenologically very easily, had been overlooked *intra vitam* owing to the fact that they had not given rise to any clinical symptoms. It was therefore decided to give every newly admitted patient a brief roentgen-ray examination, to keep records of the roentgen-ray findings, and finally to compare the latter with the clinical and later on with the necropsy findings. With the permission of Dr S. Wachsmann, at that time Medical Director of the Montefiore Home and Hospital, and with his helpful suggestions (for which most sincere thanks are expressed here), these investigations were continued for several years, in the course of which this case of myocardial calcification was discovered.

The roentgenologic side of the case has been demonstrated previously. Since then the literature on myocardial calcification has been collected, the cases so far published and the theories of the various authors have been studied and classified. The result of the work is herewith given.

In presenting the material, it was deemed advisable first to enumerate the cases published previously and then to describe as the last one of the series my own case, followed by a brief résumé of the various theories on myocardial calcification. In doing so, it is not intended to pose here as a pathologist or as a clinician, but strictly as a clinical roentgenologist, who has to have a sufficient understanding of the clinical as well as gross pathologic side of all those conditions which may come up for consideration roentgenologically, a knowledge of which ought to be con-

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\* Read before the German Medical Association of New York, Feb. 4, 1924.

† Demonstrated before the New York Physicians Association, March 6, 1919.

sidered absolutely indispensable not only for the clinical roentgenologist but for any qualified roentgen-ray specialist

For a reader's understanding of the following cases it might be well to point out here several fundamental points pertaining to calcification in general, namely (1) dead tissue, or at least deteriorated tissue, appears to be a place of predilection for calcium deposits, (2) as calcium is excreted mainly through the kidneys, intestine and bronchi, interference with its excretion in those organs may become a causative factor for abnormal calcium deposits within the body tissues, (3) freeing of large amounts of calcium within the body, for instance, by extensive bone destructive processes, may cause an overloading of the circulation by calcium salts, followed by secondary calcium deposits in apparently healthy tissues the so-called calcium metastasis of Virchow,<sup>1</sup> (4) as in the lung, the stomach, and the kidneys acids are excreted into cavities, there may be left an increased alkalinity of the fluids in the substance of the organs mentioned This increased alkalinity makes the calcium salts decidedly less soluble and may thus aid under certain conditions in the causation of calcium deposits in those organs

#### REVIEW OF THE LITERATURE

Morgagni,<sup>2</sup> in his excellent work published in 1762, briefly mentions a case of calcification of the heart He also has collected a few similar cases without giving any further details

In 1768, M Bordenave<sup>3</sup> cites the case of a man, aged 50 years, who had been suffering for a long time from cardiac insufficiency Necropsy showed a bilateral hydrothorax, adhesive pericarditis, and myocardial calcification "of unequal thickness and in some places 2 inches (5 cm) in breadth" This calcification involved the "whole of the right ventricle from the basis to the apex of the heart and following the course of the septum, ascended from the apex about half way up the left ventricle"

An interesting case of extensive myocardial calcification was published in 1783 by Samuel Foart Simmons and Henry Watson,<sup>4</sup> the former giving a review of the clinical side, the latter describing the necropsy findings The article was published in 1783 This volume is interesting not only because it contains the first well described case of myocardial calcification, together with an illustration (Fig 1) of the

1 Virchow Ueber Kalkmetastase, Virchows Arch f path Anat 8 103, 1855, 9 618, 1855

2 Morgagni De Sedibus and Causis Morborum, 1762, epist 27, art 16, etc.

3 Bordenave, M A Case of Ossification of the Heart, Mem Acad de sc, Paris, 1768

4 Simmons, S F, and Watson, H A Case of Ossification of the Heart, London Medical Communications, 1783, p 228

necropsy specimen, but also because it gives a detailed account of the great influenza epidemic of the year 1782. One is reminded, when reading that report, of the last influenza epidemic in the United States.

The patient of Simmons and Watson was a man aged 67, who had died from carcinoma of the esophagus. As he had been admitted to



Fig 1—The heart in the case of Simmons and Watson, showing distribution of calcification

the Westminster Dispensary at London at a very advanced stage of the disease, the esophageal symptoms completely dominated the clinical picture, so that no evidence suggestive of a cardiac lesion was noticed. At necropsy, on opening the abdomen, a hard mass on palpation was felt through the diaphragm which later proved to be due to an extensive

massive calcification of a large portion of the heart Watson says about the necropsy findings

"The ossification possesses that surface of the heart which rests on the diaphragm, the center of it nearly corresponding with the septum ventriculorum It extends from the basis to the very apex of the heart, is broadest in the middle, and branches out irregularly through the fleshy substance of both ventricles, over the greatest part of the auricle and for some way round the basis of the heart, following the course of the coronary vessels On searching with the finger, I could nowhere perceive that it projected within the auricle or ventricle, so that it did not appear to have diminished their capacity "

It may also be of interest to hear Watson's theory on calcification. He says "The measure of every morbid ossification will no doubt depend much on the abundance of creta in the habit That it does abound in some, and that it is very deficient in other constitutions, we are fully convinced Ossification of the heart, so far as I have been able to observe, begins in the cellular membrane, under its investing coat, in specks or thin scales, and is at first superficial It is analogous to the ossification in the the blood vessels, where the disease evidently begins in the cellular connecting medium between their coats, proceeding from within outwards, till at length the vessels are converted into complete bony tubes, such as we often find them. . It may not be improper to say, that flesh is ossified when the muscular texture is in any part totally destroyed, and its place usurped and occupied by earthy or cretacious matter, harder sometimes than bone itself " In other words, Watson thought that calcification takes place only in necrotic tissue

In 1809, Burns,<sup>5</sup> reporting a case of a thrombus in the left auricle, in a man with advanced coronary sclerosis, mentions that the flesh of the heart was "diseased with specks of bone "

Rokitansky,<sup>6</sup> 1849, briefly mentions a case of chronic cardiac lesion in which necropsy revealed advanced myocarditis with fatty degeneration The apical portion of the heart showed evidence of calcification Microscopic examination showed large number of calcium granules deposited between the partly destroyed muscle fibers

Another case was published by Heschl<sup>7</sup> in 1861 A woman, aged 30, presented the classical picture of advanced Bright's disease associated with marked cardiac involvement Necropsy revealed advanced myocardial degeneration, with deposition of calcium carbonate granules

5 Burns, A Disease of Heart, Edinburgh, 1809, p 194

6 Rokitansky Beitrag zur Kenntniss der Verknoecherungsprozesse Ztschr d k k Ges d Aertz in Wien 1 1, 1849

7 Heschl Teilweisl Verkneidung der Herzmuskulatur, Oesterr Ztschr f prakt Heilk 7 49, 1861

within broken up heart muscle fibers Heschl considers this case one of calcium metastasis as described by Virchow, notwithstanding the absence of any bone destructive process which might have caused an overloading of the blood with calcium salts The advanced renal involvement appeared to him sufficient justification for his conclusions

Coats,<sup>8</sup> in 1872, cites two cases of myocardial calcification The first patient was a man brought to the hospital in a dying condition He "evidently showed chronic bronchitis and emphysema with a possible syphilitic taint" Necropsy revealed a small pericardial effusion, extensive fatty degeneration of the heart and calcification of the apical portion of the left ventricle The calcium was deposited in the form of minute granules within the muscle fibers

His second case was a patient with relapsing fever followed by pyemia Necropsy findings consisted of multiple abscesses in various organs, marked degenerative changes in the myocardium with areas of focal necrosis, the latter presenting numerous calcium phosphate deposits in the form of granules and plaques

Coats also mentions that during his visit to Germany in 1870, he was shown by Dr Koester at Wuerzburg, a heart, the myocardium of which was impregnated with lime deposits in fine granular form He fails to give any details, nor has a report of this case ever been published

Recklinghausen,<sup>9</sup> in 1883, says briefly that he has seen cases of calcification of the myocardium similar to those published by Coats, but he fails to give any further data

Roth's<sup>10</sup> case, published in 1884, was a man aged 29, suffering from chronic traumatic osteomyelitis of the left hand followed by sepsis, associated with clinical evidence of marked renal involvement Necropsy showed calcification in the heart wall, the kidneys and the stomach Within the heart the calcium was scattered mainly throughout the ventricles in the form of fine granules deposited in degenerated muscle fibers There was marked fatty degeneration Muscle fibers presenting evidence of fatty degeneration did not, however, show any calcification

In the kidneys the calcium was found mainly in the glomeruli, to a lesser degree also in the canaliculi

In the stomach the calcium deposits were confined to the interstitial tissue of the mucosa The glandular elements were not involved

On the strength of the above findings, the case was considered by Roth one of calcium metastasis

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<sup>8</sup> Coats Two Cases of Calcareous Infiltration of Muscle Fibers of the Heart, Glasgow, M J 4 433, 1872

<sup>9</sup> von Recklinghausen Handb d allg Path d Kreisla u d Ernahrung 1883, p 302

<sup>10</sup> Roth, M Ueber Metastasen von Kalk Fett und Kohlenstaub, Kor Bl f Schweizer Aerzte 9 226, 1884

Jacobsthal,<sup>11</sup> in 1890, reports the case of a girl aged 3 weeks, who was markedly underdeveloped and icteric, in whom necropsy revealed evidence of an extensive, diffuse interstitial myocarditis associated with calcification of the anterior papillary muscle of the right ventricle.

Askanazy's<sup>12</sup> case, briefly mentioned in his work published in 1901, was a woman, aged 36, presenting the clinical picture of chronic endocarditis. Necropsy showed marked cardiac hypertrophy, calcification of coronary vessels, advanced myocarditis, irregular calcification within the wall of the left ventricle.

Langerhans'<sup>13</sup> publication (1902) contains a brief mention of a case of chronic lead poisoning, which at necropsy revealed marked calcification of the ventricles. No further data are given.

Rudis-Jicinsky's<sup>14</sup> paper on "Calcification of the Heart" could not be obtained.

Liebscher's<sup>15</sup> patient, in 1902, was a woman, aged 26, suffering from chronic pulmonary tuberculosis, chronic nephritis and cardiac insufficiency. Necropsy showed advanced myocarditis with small calcium phosphate deposits scattered throughout the heart muscle, and calcification within the liver and spleen.

Of great interest is the next case published in 1906. The clinical side was described by Leyden,<sup>16</sup> the pathologic side by Lazarus and Davidsohn. The patient was a girl, aged 19 years. The onset of the disease was sudden with pain and swelling of the joints, sweating, and rise in temperature, giving the clinical picture of acute rheumatism. At the cardiac apex there was a systolic murmur. Later, paralysis of the abducens nerve developed and the patient vomited several times. Death took place a few days later. Necropsy revealed an extensive sarcoma of the dura mater associated with advanced diffuse destruction of the tabulae of the skull. The heart was free in the pericardium, epicardium smooth, heart of the size of a fist, valves normal, the lining of the left auricle was hardened and covered with white calcareous plaques. There was extensive calcification also in the lung, kidneys and stomach. Microscopic examination showed that the calcifying changes

11 Jacobsthal. Verkalkung v Herzmuskelfasern bei einem Kinde, Virchows Arch f path Anat **159** 361, 1900.

12 Askanazy. Ueber Kalkmetastase und progressive Knoschenatrophie, Festschr z Feier d 60 Geburtst v M Jaffe, 1901, p 187.

13 Langerhans. Grundriss der Allg Path und Pathol Anat, Berlin, 1902, p 419.

14 Rudis-Jicinsky. On Calcification of the Heart, J West Surg Ass Det, 1901, p 37.

15 Liebscher. Ueber Herzmuskelverkalkung, Prag med Wchnschr **27** 180-195, 1902.

16 Leyden and Davidsohn. Hirnhautsarkom mit zahlreichen Kalkmetastasen i Herzen, Deutsch med Wchnschr **32** 601, 1906, Ztschr f klin Med **60** 314, 1906.



were confined to the endocardium, while the myocardium and epicardium appeared normal

The authors considered the case one of calcium metastasis in the sense of Virchow, and thought that in such cases lungs, kidneys and stomach form places of predilection for the deposition of calcium on account of their abundance in oxygen and acids

Topham,<sup>17</sup> in 1906, reports a case of bone formation in the myocardium in a man, aged 71, who gave the clinical picture of chronic cardiac insufficiency, and in whom necropsy revealed evidence of advanced myocarditis with fatty degeneration, and two big pieces of bone in the anterior and posterior portions of the heart muscle

At the meeting of the German Pathologic Society in 1907, Hedinger<sup>18</sup> reported two cases. The first one was a boy aged 15 years, suffering from chronic appendicitis followed by sepsis. Necropsy showed, besides the usual multiple abscesses in various organs, a large number of areas of focal necrosis within the wall of both ventricles mainly, associated with calcium deposits within the necrotic tissue.

Hedinger's second case was a man, aged 43, giving the clinical picture of chronic nephritis with marked cardiac involvement. Calcification was found to be extensive within the wall of both ventricles, the calcium being deposited within broken up muscle fibers. There was marked fatty degeneration around the calcified areas.

Hedinger explains the calcification process in his two cases on the basis of myocardial degeneration, being justified in doing so, he thinks, in view of the fact, that on careful microscopic examination he had found besides the calcified areas, numerous necrotic foci which were not calcified yet. The infrequency of published observations on myocardial calcification he explains by asserting that the fine calcified foci may quite often be overlooked at necropsy or be mistaken for something else.

In discussing Hedinger's paper, Roessle<sup>19</sup> and Fischer<sup>20</sup> report on similar findings. Roessle's case was a woman of middle age, who had died from uremia and in whom necropsy revealed findings closely similar to those described by Hedinger, the calcification being secondary to chronic myocarditis. Fischer's case was an infant, aged several weeks presenting during lifetime evidence of marked cardiovascular disturbance. Necropsy showed advanced endocarditis and myocarditis with fatty degeneration. Calcified foci were scattered throughout the entire heart muscle and were most dense in the papillary muscles.

17 Topham. Bone Formation in the Heart, *Brit. M. J.* **2** 953 (Oct. 13) 1906

18 Hedinger. Ueber Herzverkalkung, *Verhandl. d. deutsch. path. Gesellsch.* **10** 295, 1907-1908

19 Roessle. *Verhandl. d. deutsch. path. Gesellsch.* **10** 303, 1907-1908

20 Fischer. *Verhandl. d. deutsch. path. Gesellsch.* **10** 228, 1907-1908

Wiechert,<sup>21</sup> in 1907, reported the case of a man, aged 48, who three days after eating fish had developed the clinical picture of sepsis and had died twenty days later. The case proved to be one of *B. paratyphosus* infection. On cross section, one found at the basal portion of the left ventricle the myocardium studded with small, pinhead sized, yellowish-gray, hard nodules which later on proved to be due to calcium phosphate deposits within necrotic muscle fibers. Besides the heart, calcification was found within the kidney, especially within the canaliculi and glomeruli. Wiechert considers the calcifying process in his case as secondary to myocardial degeneration of bacterial origin.

In 1909, Siebenmann<sup>22</sup> reported a case of a man, aged 36, who had suffered from advanced osteomalacia with extensive cystic degeneration of the long bones, chronic nephritis and cardiac insufficiency. Extensive calcification was found in this instance in the heart, kidneys, lung and liver. Within the wall of the left ventricle calcium phosphate was deposited in the form of fine granules as well as in the form of plaques in degenerated heart muscle fibers mainly, to a lesser degree also in the interstitial tissue, being most abundant around the vessels suggesting, according to the author, the probability that the calcium had been brought in by the blood stream. In the kidneys, the calcium was seen mainly within the canaliculi and the glomeruli, within the lung in the elastic tissue especially, within the liver in the middle portions of the acini. Siebenmann considers the case one of plain calciummetastasis in the sense of Virchow, being secondary to the bone dissolving osteomalacic process.

Hart's<sup>23</sup> case, published in the same year, is a woman, aged 24, with the clinical diagnosis of hereditary syphilis. The heart, on necropsy, presented evidence of fatty degeneration and a large number of necrotic foci, the latter containing calcium deposits in fine granular form. The calcification was confined strictly to the necrotic muscle fibers, the healthy muscle fibers being free from calcium deposits. Hart thinks that there is a definite relationship between the death of the cell and the deposition of calcium, and he believes that calcification does not take place in healthy tissue.

Of special interest and importance is the case of Veisé,<sup>24</sup> in the year 1910. It presents a striking similarity to that of Leyden. A man, aged 25, had suffered from chronic myelogenous leukemia for a period of two

21 Wiechert, A. Ueber einen Fall von Paratyphus B mit Herzmuskelverkalkung, Inaugural Dissertation, Marburg, 1907.

22 Siebenmann, F. Ueber Verkalkung der Herzmuskulatur. Inaugural Dissertation, Basel, 1909.

23 Hart, C. Die Herzmuskelverkalkung, Frankfurter Ztschr. f. Pathol. 3: 706, 1909.

24 Veisé. Ueber ausgedehnte Verkalkg. d. Lunge, Lungenvene u. d. linken Vorhofs bei chron. myelogen. Leukaemie, Verhandl. d. deutsch. path. Gesellsch. 14: 281, 1910.

and one-half years, presenting at times a clinical picture suggestive somewhat of acute rheumatism. Calcification was found to be present in the heart, the lungs and kidneys. In the heart, the calcifying process was confined exactly as in Leyden's case, to the endocardium and the sub-endocardial connective tissue of the left auricle. The other layers of the heart wall presented no abnormality. The accumulation of the calcium in the lung and kidneys was of the type described in some of the previous cases. Here again calcium in fine granular form was found mainly in the canaliculi and glomeruli of the kidneys, and in the elastic tissue of the lung, the elastic tissue "evidently being a place of predilection." Verse considers his case one of true calcium metastasis. The large amount of calcium salts made free by the leukemic process overloaded the circulation, the overload being deposited in the organs before mentioned. The fact that the calcification process in the auricles was confined to the endocardium, while the other parts of the heart wall were free from any changes, in other words, that the interior of the auricles practically was lined with calcium, suggests the probability that the calcium was taken up by the endocardium directly from the contents of the auricles, in other words, that the endocardial lining of the auricles was impregnated with calcium salts. Verse therefore concludes that the term "calcium metastasis" is, for his case at least, not a quite correct one, but that "heteroplastic calcium impregnation" would be a more proper designation of the process involved.

The findings in Pappenheimer's<sup>25</sup> case, concern a man, aged 21, in whom chronic sepsis had developed after an operation for gangrenous appendicitis. Necropsy revealed suppurative pyelophlebitis, thrombosis of the portal vein, multiple abscesses in various organs, and numerous areas of focal necrosis within the myocardium of the left ventricle mainly. Calcification was present in the left ventricle, the liver, lung, and kidneys. In the heart the calcifying process was confined strictly to the areas of focal necrosis where calcium phosphate was seen deposited in the form of fine granules within greatly degenerated muscle fibers while healthy muscle fibers failed to present any calcification. There was no sign of inflammation, so that the lesion is definitely on a noninflammatory basis. The case, according to Pappenheimer, is one of toxic necrosis of heart muscle fiber followed by calcium deposits. Fatty degeneration, though present, did not seem to have any definite relation to calcification.

Tilp,<sup>26</sup> in 1912, describes the findings in a man, aged 28, who had been suffering from bronchiectases for two years. Gradually an empyema of the left side of the chest developed, for which an operation was done.

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<sup>25</sup> Pappenheimer, A. Calcification of the Heart Muscle Fibers, *Proc New York Path Soc* **10** 129, 1910.

<sup>26</sup> Tilp. Herdfoermige Verkalkung des Myocardium bei Sublimatvergiftung, *Verhandl d deutsch path Gesellsch* **15** 471, 1912.

This was followed by an attempt on the part of the patient to commit suicide by drinking 40 c c of a 5 per cent solution of bichlorid of mercury. This again was followed by aneuria, icterus, diarrhea, cold sweats, coma, and death on the fifth day. Necropsy revealed within the myocardium of the left ventricle, especially in the region near the cardiac apex, numerous areas of focal necrosis containing calcium deposits. The calcification similar to the findings in Pappenheimer's case, was strictly confined to the necrotic heart muscle fibers. The kidneys presented the classical picture of "sublimatiere" (sublimate kidney) with calcium infarcts. Tilp points out that the myocardial calcification in this case is something very unusual, in view of the fact that in experimental "sublimatiere" with calcium infarcts in rabbits myocardial calcification has never been encountered.

The next case, published in the same year by Oppenheimer,<sup>27</sup> is of extreme interest and at the same time quite puzzling. A man, aged 44, presenting the clinical picture of mitral stenosis with auricular fibrillation, showed at necropsy an extensive calcification of the inner coat of the left auricle proper, so that the whole of the latter, except the auricular appendix and the interauricular septum, felt like a bony plate. Microscopic examination revealed that a portion of this plate was undergoing an osteogenetic process.

As to the further pathologic details in this case Oppenheimer says "Only three blocks of tissue from the hard left auricular wall were sectioned, and in one of these we encountered an area undergoing ossification. This area presents both calcified and noncalcified osteoid tissue. The hard plate in the left auricular wall consists of hyaline degenerated connective tissue much of which is calcified. The lime deposit is distributed throughout the inner coat of the left auricular chamber and the inner coat only, leaving the striated muscle untouched. For the most part it is in the shape of scattered granules and plaques bordered by coarse granules, but also, though more rarely, it is in the form of nodules possibly representing calcified atheromatous patches. There was fat present throughout most of the section, but not much in the calcified areas, so that no relation between the deposit of lime and a previous infiltration of fat is indicated. The test for amyloid proved negative.

"Though we believe that the deposit of lime was conditioned by the local hyaline degeneration of the cardiac tissue, we must admit the possibility that an increased calcium content of the circulating body fluids may account for the lime deposits in the left auricle. We grant this

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27 Oppenheimer, B. S. Calcification and Osteogenic Changes of Left Auricle in a Case of Auricular Fibrillation, *Proc. New York Path. Soc.* 12: 213, 1912.

possibility because we were unable to exclude it by an examination of the excretions during life or of the bones at necropsy. On the other hand, in our case sections of lung, kidney, liver and spleen, free of lime salts as they are, indicate that calcium metastasis played no rôle."

At the first sight it would seem that the findings in Oppenheimer's case may nullify our reasoning as expressed here, with regard to calcium impregnation of the endocardium of the left auricle in cases of calcium metastasis. It must be admitted that one might very easily be induced to consider this case as one of calcium metastasis. And yet it is not so, because the endocardial calcification process in calcium metastasis consists in the precipitation of calcium salts into the endocardial layers of an otherwise perfectly normal heart wall in patients with evidence of extensive bone destructive processes. Different are the conditions in Oppenheimer's case. On one hand, there is no evidence of any bone destructive process which could account for a possible overloading of the body fluids with calcium salts, on the other hand, satisfactory explanation for the calcifying process is given by the presence of hyaline degeneration associated with deposit of fat not infrequently observed in beginning atherosclerosis as found in the blood vessels, in cardiac valves, much less frequently, according to Kaufmann, in the endocardium of the auricle, sometimes also of the ventricle, a process which is followed rather frequently by calcification, as hyalinized connective tissue attracts calcium salts quite readily. Oppenheimer therefore was justified in not classifying his case as one of calcium metastasis, but explaining the calcifying process on a retrogressive basis. This case, therefore, will be placed in our classification table into the column of "myocarditis" with the understanding that the retrogressive changes present are of the foregoing type specified.

Krayn,<sup>28</sup> in 1914, wrote an inaugural dissertation on "Herzverkalkung." His case is a woman, aged 54, presenting the clinical picture of a double mitral lesion, associated with marked cardiac hypertrophy and dilatation, decompensation and renal insufficiency. Small calcified foci were found scattered throughout the entire myocardium. The calcium was deposited within broken up heart muscle fibers either in the form of fine calcium carbonate granules or small plaques. Healthy muscle fibers failed to show any calcification. Evidence of fatty degeneration was present in calcified and noncalcified fibers. The kidneys were of the granular contracted type. The findings in this case are explained by Krayn on the basis of interference with the calcium excretion in the kidneys, followed by secondary calcium deposits within the necrotic areas of the myocardium.

<sup>28</sup> Krayn, M  
Heidelberg, 1914

Ueber Herzmuskelverkalkung. Inaugural Dissertation,

In 1915 Bergamowitch<sup>29</sup> published two cases of calcification of the heart muscle. No further data can be given, as the original article could not be obtained.

#### REPORT OF CASE

My own case was a man aged 74, a Russian married, peddler by occupation who was admitted to the Montefiore Home April 30, 1917 where he died July 11 1917. His family history was negative. His personal history showed he was an excessive smoker, he did not drink, he was a strenuous worker all his life, he had no children and his wife had no miscarriages. The previous history: Syphilis was denied, the patient had had gonorrhea at 18 otherwise the history was negative.

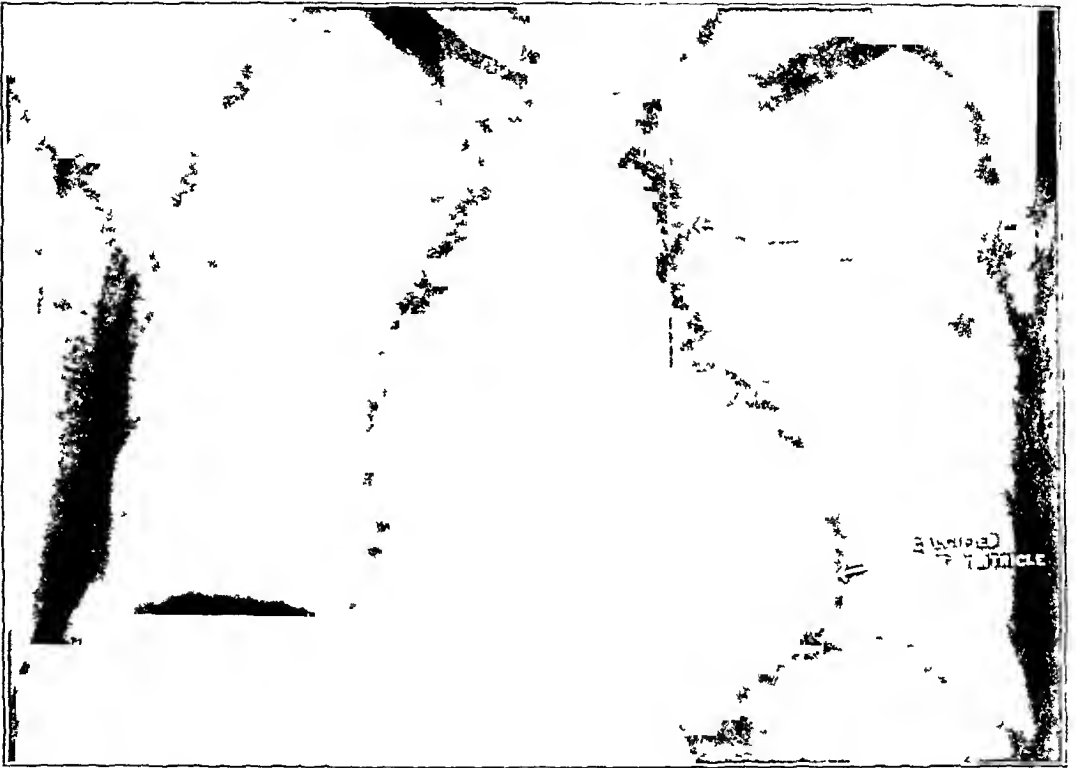


Fig 2—Postero-anterior roentgenogram of the chest of my patient taken intra vitam, showing the ring-like shadow within apical portion of the heart, and the oval shaped shadow within the bulbous aorta.

*Present Illness*—Sudden onset eighteen months ago, with loss of consciousness and speech stupor involuntary urination and defecation. No convulsions. He was confined to bed for two months and the recovery was gradual. Since then he had a chronic cough, expectoration, swelling of the feet and dyspnea on slight exertion.

*Physical Examination*—Evidence of chronic emphysema, advanced arteriosclerosis, moderate cardiac insufficiency and bilateral inguinal hernia were present.

Roentgenologic examination of the chest was made on June 14. Fluoroscopy revealed marked diffuse fibrosis throughout the median portions of both lungs, hyperaeration of basal portions, low position of diaphragm, poor diaphragmatic excursions, moderate enlargement of heart to left, very superficial left ventricular contractions, increased bulging of aortic arch. The roentgenogram showed a fine, ring-like shadow, about 3.5 cm. at its widest diameter, occupying

<sup>29</sup> Bergamowitch. Two Cases of Calcification of the Heart, Sibirsk-Vrach, Tomsk, 1915.

the apical portion of the heart (Fig 2) There were other oval shaped shadows within the aortic arch Roentgenologic conclusions were chronic lung fibrosis, moderate cardiac enlargement, suggestion of myocardial involvement, calcium plaques in wall of aortic arch, suggestion of calcification within the shadow of the cardiac apex, either in the pericardium or myocardium

Roentgenologic reexamination was made on June 17 Plates of the heart were taken with the aid of small diaphragm intensifying screens and instantaneous exposures, with the patient in various postures The entire calcified area in the region of the left ventricle could be demonstrated very definitely From the various plates taken at various angles it could be well seen that the calcifying process solidly involved the entire apical portion of the heart (Fig 3)

The patient died several weeks later from an incarcerated hernia

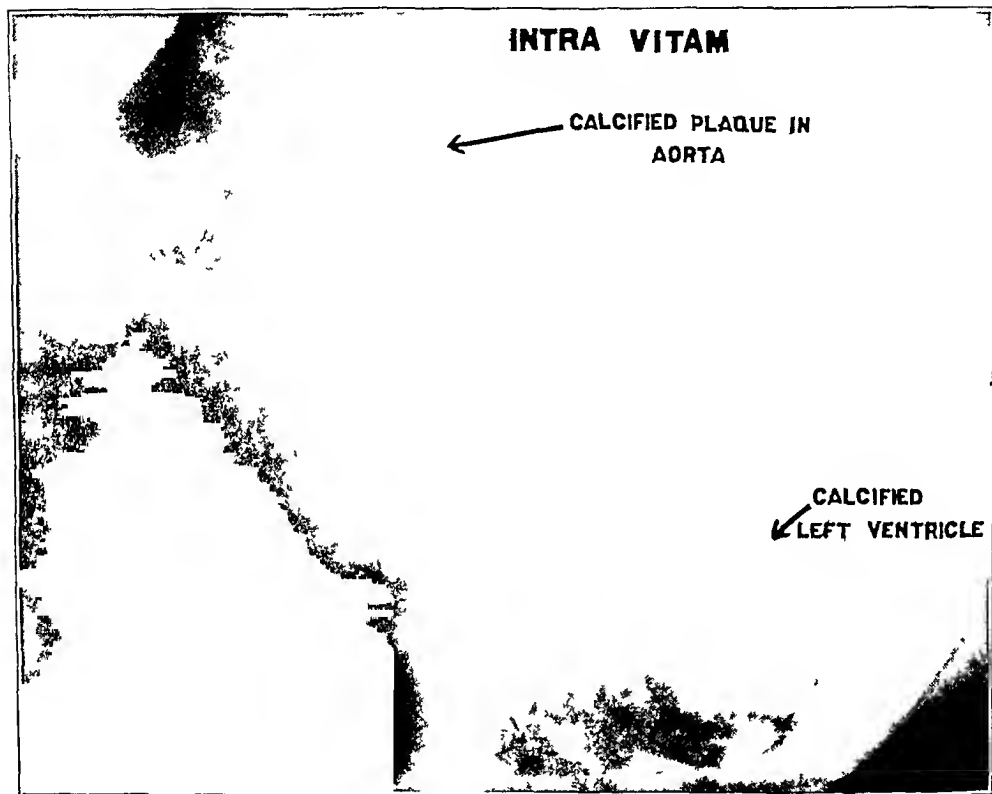


Fig 3—Intra vitam roentgenogram of the cardiac region taken with the patient in an oblique posture, showing the entire calcified area within the apical portion of the heart

*Necropsy*—The heart weighed 550 gm and was somewhat enlarged, on palpation through the pericardium a very hard mass was felt over the entire apical surface, the pericardium was adherent by fibrous tissue over the anterior and left surfaces Left auricle the endocardium was white and milky, in the anterior leaflet of the mitral valve was a small, hard calcified plaque Left ventricle in its lower half was a cup shaped area of complete calcification (Fig 4), extending 5 cm from the apex on the anterior surface, 3.5 cm on the diaphragmatic surface and 4 cm on the interventricular surface The ventricular aspect of this calcified cup was irregular and marked by shallow depressions and elevations Otherwise, it was evidently covered by smooth endocardium The external aspect was covered by thin layers of fibrous pericardium The coronary arteries were thickened, slightly tortuous calcified to veritable pipe stems, the lumen of the left coronary was almost completely occluded, leaving a passage about as thin as a hair Aorta

a number of calcified plaques were in its ascending and transverse portions. Microscopic examination showed that within the calcified area very little muscular tissue was in evidence. The heart muscle cells were broken up by masses of dense scar tissue. The calcium (phosphate) was found deposited in the form of irregular plaques.

We have here, therefore, a case in which calcium has been deposited in large quantities within the necrosed apical portion of the heart following a gradually complete obliteration of the left coronary artery. It is interesting to note that here, as in the case of Simmons and Watson, the patient was able to carry on a moderately bearable life notwithstanding the fact that a large portion of the left ventricle had been practically put out of commission.

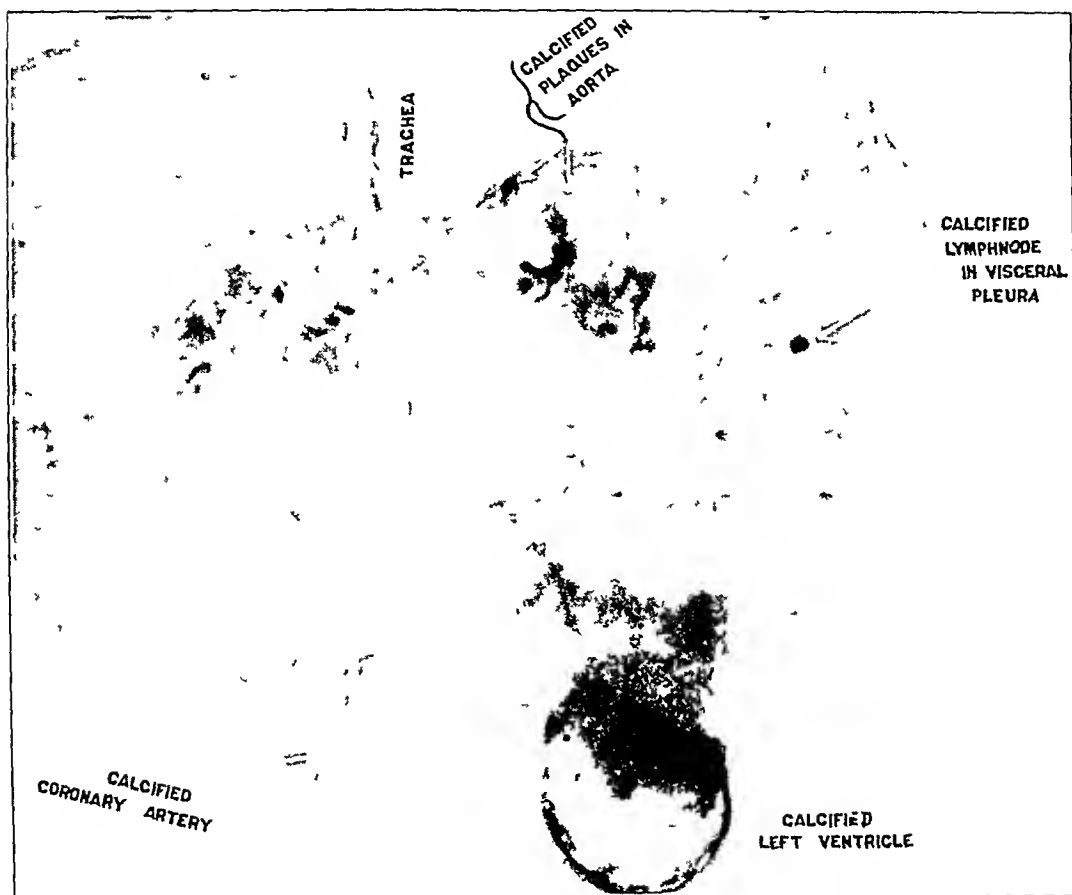


Fig 4—Roentgenogram of the necropsy specimen

#### ROENTGENOLOGIC ASPECT OF CALCIFICATION OF THE HEART

Roentgenologic literature on calcification of the heart and its demonstration *intra vitam* is extremely scanty. There are only two previous instances on record in which a roentgen-ray diagnosis of calcification in the heart itself was made during lifetime, namely, the cases of Groedel<sup>30</sup> and Le Wald<sup>31</sup>. Unfortunately, however, in neither one of those cases

30 Groedel, F. M. Erste Mitteilung ueber die Differenzierung einzelner Herzhoehlen im Roentgenbilde und den Nachweis von Kalkschatten i d Herzsilhouette *intra vitam*. Fortschr a d Geb d Roentgenstrahlen **16** 337, 1911.

31 Le Wald, L. Discussing this Paper at the German Medical Society, New York, Feb 4, 1924.



was a necropsy obtained, so that the final diagnosis can only be surmised. Our case, therefore, is the first one in which calcification of the heart itself was demonstrated roentgenologically *intra vitam*, was differentiated from calcification of the pericardium and in which the roentgenologic diagnosis was confirmed by necropsy. The cases published by Simmonds<sup>32</sup> concern roentgenograms of necropsy specimens.

In contrast to myocardial calcification, roentgenologic literature on pericardial calcification is quite abundant, as is shown by the publications of Rieder,<sup>33</sup> Schwarz,<sup>34</sup> Klason,<sup>35</sup> Mueller,<sup>36</sup> Weil,<sup>37</sup> Case<sup>38</sup> and others. A similar case with necropsy findings was demonstrated by me<sup>39</sup> several years ago. Though it is not the purpose of this paper to deal with roentgen-ray findings in calcifying pericarditis, this subject must briefly be touched on here for differential diagnostic purposes.

In cases where the calcifying process involves diffusely the entire pericardial sac, the calcified plaques within the anterior and posterior portions of the pericardium may or may not be shown on the usual front view plates, while the tangentially increased diameter of the calcified plaques along the lateral aspects of the heart will document themselves in the form of dense, bandlike shadows running just outside of and parallel to the heart shadow proper. In such cases a roentgenologic diagnosis of pericardial calcification is justified. In cases where only the anterior or posterior portion of the pericardial sac is calcified, the usual front view plates may present round, or ringlike or diffuse shadows within the heart shadow proper. In such instances and if front view plates only have been taken, one is not justified in making a definite diagnosis of pericardial calcification, because there is in the appearance of such shadows nothing which would differentiate them from those cast by myocardial calcification. Yet one may, even in such cases, arrive at a certain degree of differentiation between these two conditions by taking plates with the patient in various postures. If the case is one of pericardial calcification one may thus obtain a certain view in which the pericardial plaques are struck by the roentgen-ray tangentially, and thus present themselves as the bandlike dense shadows just outside of the

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32 Simmonds. Ueber den Nachweis von Verkalkungen am Herzen durch das Roentgenverfahren, *Fortschr a d Geb d Roentgenstrahlen* **12** 371, 1908

33 Rieder. Panzerherz, *Fortschr a d Geb d Roentgenstrahlen* **20** 50, 1913

34 Schwarz. Die Roentgenuntersuchungen des Herzens und der grossen Gefaesse, Leipzig, 1911

35 Klason. Pericarditis calculosa und Herzverkalkung, *Acta Radiol* **1** 162, 1921

36 Mueller. Perikardiale Verkalkung, *Fortschr a d Geb d Roentgenstrahlen*, **25** 231, 1918

37 Weil. Panzerherz und Pick'sche Lebercirrhose, *Fortschr a d Geb d Roentgenstrahlen*, **23** 489, 1916

38 Case, J. T. Pericarditis Calculosa, *J A M A* **80** 236 (Jan 27) 1923

39 Scholz, T. New York Physicians Association, March 6, 1919

heart area proper, as described above. Or one may, like in my case, by means of the various views, succeed in demonstrating that the calcifying process involves the heart proper. It might therefore be not quite advisable and even prove misleading to interpret abnormal shadows within the heart area somewhat indiscriminately at one time as myocardial, at another time as pericardial calcification without having a justification, in form of necropsy control, for so doing.

Calcification within the bulbus aorta can be diagnosed by roentgen ray very easily. Even calcified plaques within the descending aorta may be visualized by taking plates with the patient in an oblique posture. They present themselves on the plate as narrow, somewhat lengthy shadows running longitudinally just in front of the spine. Here too, apparently only those plaques are demonstrable which happen to be struck by the roentgen ray tangentially, whereby the diameter of the individual plaque is increased.

Large calcified areas within the heart muscle itself, as in my case, may be visualized by roentgen ray *intra vitam*. The use of double intensifying screens, small diaphragms, various postures of the patient, rapid, but at the same time sufficient, exposures will aid in obtaining desirable results. Small, fine calcified foci, for obvious reasons, cannot be demonstrated during life time with our present machinery. Possibly we will be able to do so after a further development of the roentgen-ray technic.

In necropsy specimens one is able to demonstrate by means of the roentgen ray the most minute calcified foci within the heart as well as within practically any other part of the body, as Simmonds has shown and as my own experience indicates. In the heart, for instance, it is advisable to slice up the specimen, to spread it apart and then to place it flatly on the plate. Soft tubes and slow developer should be used. As a quick and accurate localizer of small calcified areas or of any other small, localized gross pathologic changes such as produce roentgenographically sufficient differentiation of tissue densities, the use of the roentgen ray ought to be considered of very great importance for the pathologist. It is to be regretted that the roentgen ray is not universally used yet for such purposes. The results of my necropsy roentgen-ray investigations, which had been carried out on a large scale during the years from 1914 to 1920, which work will soon be published, tend to show that if roentgen ray was employed during necropsy work systematically, calcification of the heart and some other supposedly very rare conditions would be found to be more frequent than is believed at the present time. The importance of the roentgen ray for gross pathologic studies is so great that there is no doubt that every department of pathology will have a complete roentgen-ray outfit of its own, once pathologists realize what possibilities may be opened up by this new aid

## CLASSIFICATION OF CASES OF MYOCARDIAL CALCIFICATION

Going very briefly over the cases enumerated in Table 1, taking as a guide the pathologic conditions found at necropsy, omitting those cases in which the authors failed to give satisfactory data, and ignoring for the present the finer points pertaining to myocardial calcification, one may for practical purposes be justified in classifying the cases so far published in the manner given in Table 2

The first column contains all those cases which have in common one and the same stigma of myocardial degeneration, namely, myocarditis. This process may be diffuse or localized. In the vast majority of the cases it is expressly pointed out by the authors that the calcium containing muscle fibers were broken up or entirely destroyed. In some other instances microscopic examinations have not been made at all, or evidently were not made carefully enough. We then have to be satisfied with the macroscopic necropsy evidence of a retrogressive metamorphosis within the myocardium. In none of the cases where careful microscopic examinations were made, has it been found that calcification has taken place in healthy muscle fibers. Of extreme interest in this connection are the findings in the case of Jacobsthal<sup>11</sup> (Table 1, No. 10) where the myocarditic process, as well as the calcifying changes, were strictly confined to the anterior papillary muscle of the right ventricle. The primary cause of the myocarditis is of secondary importance. The calcifying process in this type of case consists of deposition of fine granules of calcium, usually calcium phosphate, within the destroyed heart muscle fibers. As these calcium granules gradually coalesce, forming smaller and larger plaques, the calcifying process may also involve the neighboring interstitial tissue. Occasionally, an osteogenetic process may develop within the calcification area and real bone may be formed similar to that found in the cases of Topham<sup>17</sup> and Oppenheimer,<sup>27</sup> for reasons not definitely known yet.

Into the second column have been placed the cases in which, owing to obliteration of the coronary artery, usually the left one, a large area of the heart wall has been rendered useless, has become dead tissue and then was gradually impregnated with calcium salts. Here the calcifying process gradually takes on a massive solid form involving a large area, and all the elements of the heart wall. It may be worth while noting that this apparent elimination of so large a portion of the heart muscle causes very little distress to the patient unless the conductive system of the heart happens to be interfered with by the calcifying process.

The third column contains the cases of chronic sepsis in which the septic process had caused, besides the usual multiple abscesses in various organs, numerous areas of focal necrosis within the myocardium. In

these instances the calcifying process is strictly confined to the areas of focal necrosis, while the other healthy portions of the heart muscle fail to present any calcium deposits. The causative factors of the septic process and possible accidental combination with another causation are of no importance for the consideration of our subject of myocardial calcification. Thus in Tilp's <sup>20</sup> case one has to eliminate the bichlorid poisoning (in the patient's attempt to seek relief from his septic disease by committing suicide) as the primary cause of the myocardial calcification. Tilp's surprise to find in a case of bichlorid poisoning a combination of a classical "sublimatnere" with myocardial calcification, something never observed before, was therefore not quite justified, because the bichlorid poisoning had nothing to do with the calcification within the heart wall, which would have been seen at the necropsy just as distinctly without the suicide attempt. Here, too, the calcium is deposited in the form of fine granules within the destroyed muscle fibers only. These granules may gradually coalesce, forming plaques. On cross section through the involved heart muscle, one sees macroscopically small areas of pin-head size and even more minute ones, yellowish-gray, slightly prominent and somewhat hard to touch.

Of special interest is column four, representing the cases of so-called calcium metastasis of Virchow <sup>1</sup>. The latter published, in 1855, a series of five cases which clinically presented the picture of an extensive bone destructive lesion, be it diffuse bone carcinomatosis, or sarcomatosis, or osteomalacia, etc., superimposed to a certain degree by a second clinical picture somewhat suggestive of acute rheumatism. Necropsy examination showed, besides the bone destructive process, extensive calcium deposits within the lung, the kidneys and the stomach. In the lung, the elastic tissue was the place of predilection for the calcium deposits, in the kidneys and the stomach the epithelial elements. It would be too lengthy to go into the details of the interesting description of the findings given by Virchow. Suffice it to say that Virchow thought that the large amounts of calcium salts made free by the diffuse bone destructive processes overloaded the circulation to such an extent that the usual provisions for calcium excretion became inadequate to their task, the overload of calcium salts being then deposited, or rather precipitated, directly within the otherwise healthy organs before mentioned. There were no calcium deposits in the heart. If one accepts the view that the cases of Virchow are classical instances of calcium metastasis, one must place in our series of heart calcification the cases of Leyden <sup>16</sup> and Versé <sup>24</sup> into the same category. Here, too, we have a bone destructive process, a clinical picture of the latter finally superimposed to a certain extent by another one somewhat suggestive of acute rheumatism, and finally calcium deposits within kidneys, lung and stomach in one case and

TABLE 1—A Brief Review of Clinical, Pathologic and Anatomic Findings in all the Published Cases

No	Year	Author	Patient's		Clinical Features	General Condition of Heart	Necropsy Findings					Involved Elements of Heart
			Sex*	Age, Years			Heart	Kidneys	Lung	Stomach	Other Organs	
1	1768	Bordenave	♂	50	Chronic cardiac insufficiency	Advanced myocarditis, adhesive pericarditis	Massive calcification of right ventricle	—	—	—	—	All elements
2	1783	Simmons and Watson	♂	67	Carcinoma of esophagus	Chronic myocarditis	Massive calcification along septum	—	—	—	—	
3	1809	Burns	♂		Advanced arterio sclerosis, coronary sclerosis	Thrombosis of left auricle, calcification of coronary arteries, chronic myocarditis	Irregular massive calcification of left ventricle	—	—	—	—	
4	1849	Rokitansky			Chronic cardiac lesion	Advanced myocarditis, fatty degeneration	Calcium granules in apical portion	—	—	—	—	Destroyed muscle fibers only
5	1861	Heschl	♀	30	Advanced Bright's disease cardiac insufficiency	Advanced myocarditis, degeneration	Diffuse in form of granules	—	—	—	—	Destroyed muscle fibers only
6	1872	Coats	♂		Chronic bronchitis, "syphilitic taint"	Pericardial effusion, generation	Calcium granules in apical portion	—	—	—	—	Degenerated muscle fibers
7	1872	Coats			Relapsing fever sepsis	Extensive fatty degeneration	Calcification of areas of focal necrosis	—	—	—	—	
8	1870	Koester (mentioned by Coats)					Diffuse impregnation of myocardium with calcium granules	—	—	—	—	Degenerated muscle fibers
9	1884	Roth	♂	29	Chronic osteomyelitis, sepsis, renal insufficiency	Chronic myocarditis, fatty degeneration	Calcium granules in ventricles mainly	Glomeruli and canaliculi	—	Mucosa	—	
10	1890	Jacobsthal		3 weeks	Syphilis (?)	Localized interstitial myocarditis of anterior papillary muscle of right ventricle	Calcium granules in anterior papillary muscle of right ventricle	—	—	—	—	All elements
11	1901	Askanazy	♀	36	Chronic endocarditis	Cardiac enlargement, calcification of coronary vessels, advanced myocarditis	Massive calcification within wall of left ventricle	—	—	—	—	
12	1902	Langerhans			Chronic lead poisoning		Ventricles	—	—	—	—	
13	1902	Liescher	♀	26	Chronic pulmonary tuberculosis, chronic nephritis, cardiac insufficiency	Advanced myocarditis	Diffusely scattered calcified foci	—	—	—	Liver, spleen	Degenerated muscle fibers

14	1906	Jevdon and Lazarus	♀	19	Sarcoma of dura with eminent ple ture suggestive of acute rheu- matism	Normal myocar- dium and epi- cardium	Calcification of endocardium of auricles	Glomeruli and capil- lari	Plastic tissue mainly	Muscle	—	Endocardium only
15	1906	Topham	♂	71	Chronic cardiac insufficiency	Advanced myocar- dial atrophy, fatty degeneration Areas of focal necrosis	Bone plates in ante- rior and posterior heart wall	—	—	—	—	—
16	1907	Hedinger	♂	15	Chronic appendi- citis, sepsis	—	Calcium deposits within areas of focal necrosis of both ventricles	—	—	—	—	—
17	1907	Hedinger	♂	13	Chronic nephritis, cardiac insuffi- ciency	Chronic myocar- dial atrophy	Calcium granules within destroyed muscle fibers	—	—	—	—	Degenerated muscle fibers
18	1907	Roessle	♀	Middle age	Uremia	Chronic myocar- dial atrophy	Diffuse calcium deposits	—	—	—	—	—
19	1907	Fischer	—	Infant	Cardiovascular disturbance	Multiple valvular lesion, endocarditis, myocarditis, fatty degeneration	Diffuse calcium deposits, mainly in papillary muscles	—	—	—	—	—
20	1907	Wiechert	♂	18	Paratyphus B sepsis, renal insufficiency	Numerous areas of focal necrosis	Calcium deposits within areas of focal necrosis	Glomeruli and capil- lari	—	—	—	Degenerated muscle fibers
21	1909	Siebenmann	♂	36	Advanced osteo- malaria, chronic nephritis, cardiac insufficiency	Chronic myocar- dial atrophy	Diffuse calcifica- tion in form of granules and plaques in left ventricle	Glomeruli and capil- lari	Plastic tissue mainly	—	Liver	—
22	1909	Hunt	♀	21	Congenital syphilis	Fatty degenera- tion, numerous necrotic foci	Calcium in granules within destroyed muscle fibers	—	—	—	—	Degenerated muscle fibers
23	1909	Veise	♂	25	Chronic myelogen- ous leukemia with cystic bony de- struction	Normal myocar- dium and epi- cardium	Endocardium of auricles impreg- nated with calcium	Glomeruli and capil- lari	Plastic tissue mainly	—	—	Endocardium only
24	1910	Pappenheimer	♂	21	Gangrenous appen- dicitis, sepsis	Areas of focal necrosis	Calcium granules within areas of focal necrosis	Glomeruli and capil- lari	Plastic tissue mainly	—	Liver	Degenerated muscle fibers only
25	1912	Tipp	♂	28	Bronchoectasis, empyema lung, chest, sepsis, blebroid	Areas of focal necrosis	Calcium deposits within areas of focal necrosis	“Sublun- gular” with calcium infarcts	—	—	—	Degenerated muscle fibers only
26	1912	Oppenheimer	♂	11	Poisoning Anular fib- rillation	Hyaline degenera- tion of endocard	Calcium and be- ginning bone forma- tion of endocard	—	—	—	—	Endocardium only
27	1911	Krayn	♀	51	Mitral stenosis, cardiac and renal insufficiency	Chronic myocar- dial atrophy	Calcium deposits within degenerated muscle fibers	—	—	—	—	Degenerated muscle fibers only
28	1915	Berganowitch	—	—	—	—	—	—	—	—	—	—
29	1915	Berganowitch	—	—	—	—	—	—	—	—	—	—
30	1921	Scholz	♂	71	Advanced arterio- sclerosis	Advanced calcifica- tion of coronary arteries, diffuse myocarditis	Massive calcifica- tion of apex	—	—	—	—	All elements

\* In this column, ♀ indicates female, ♂, male

within the kidneys and lung in the other case, and within the endocardium of the auricles in both cases. The character of the calcium deposits corresponds to that described by Virchow. The calcification process in the endocardium of the auricles, though not present in Virchow's, but present in both Leyden's and Versé's case, also would fit very perfectly into the classical picture of calcium metastasis: the endocardium of an otherwise perfectly normal heart impregnated with calcium salts. One should bear in mind that in true calcium metastasis or rather "heteroplastic calcium impregnation" the calcifying process is produced by direct deposition of calcium salts from the calcium-oversaturated fluids into the adjacent but normal tissue elements. There must, therefore, be in the calcified organs themselves no pathologic changes which could

TABLE 2—*Classification of Cases of Calcification of the Heart*

1	2	3	4 Calcium Metastasis		5
Myocarditis	Obliteration of Coronary Arteries	Sepsis	(a) Pure Calcium Metastasis Involving Endocardium Only	(b) Combined with Myocarditis Causing Calcification of Myocardium	Direct Extension from Calcifying Pericarditis
1 Bordenave	1 Burns	1 Coats II	1 Leyden	1 Roth	1 Diemer
2 Simmons	2 Askanazy	2 Hedinger I	(sarcoma of dura)	(chronic osteomyelitis)	2 Obendorfer
3 Rokitansky	3 Scholz	3 Wiechert	2 Versé	2 Siebenmann	3 MacFarland
4 Heschl		(Paratyphus B)	(myelogenous leukemia)	(osteomalaria)	4 Lucys
5 Coats I		4 Pappenheimer			
6 Jacobsthal		5 Tulp			
7 Liebscher		(bichlorid poisoning)			
8 Topham					
9 Hedinger II					
10 Roessle					
11 Fischer					
12 Hart					
13 Oppenheimer					
14 Krayn					

possibly account for the calcium deposits. If one applies this standard to the cases of Roth and Siebenmann, both of which are classified by the authors as instances of calcium metastasis, one must immediately admit that neither one of these cases can be considered as true calcium metastasis, so far as the myocardial calcification process is concerned, because in both instances necropsy revealed evidence of advanced myocarditis, which latter, per se, would fully account for calcium deposits. Furthermore, the type of calcification, in the form of fine granules within destroyed heart muscle fibers, is here quite different from that in Leyden's and Versé's cases in which the calcium directly impregnated the endocardium of the auricles. Roth's<sup>10</sup> and Siebenmann's<sup>22</sup> cases therefore belong, from the point of myocardial calcification, to the myocarditis cases of the first column, though it has to be admitted that from the point of their renal, gastric and pulmonary calcification, and also in view of the presence of an extensive bone destructive process,

they belong to the class of calcium metastasis. These latter classic features of calcium metastasis may, but must not necessarily, have aided in the production of calcium deposits within the degenerated myocardium in Roth's and Siebenmann's cases.

In covering the various types of calcification of the heart, one has to include the cases in which calcification of the myocardium has been produced by direct extension of the calcifying process in calculous pericarditis. Some of such instances, like the cases of Diemer,<sup>40</sup> Oberndorfer,<sup>41</sup> McFarland<sup>42</sup> and Lucas,<sup>43</sup> where the authors have furnished careful microscopic reports, have been collected in column five. These cases are of great importance in the consideration of the causative factors of our subject, because the microscopic sections reveal how the completely adherent calcified pericardium causes by direct pressure first atrophy of the epicardium, then this pressure atrophy is followed by deposition of fine calcium granules within the atrophied area, how these latter calcified areas again cause pressure atrophy of the adjacent heart muscle fibers, which again is followed by depositions of calcium granules within the broken up muscle fibers, and how this calcifying process gradually may extend deep into the myocardium, always selecting degenerated, never healthy, muscle fibers as steps in its gradually advancing invasion. These findings seem to be an additional proof for the belief that calcification of the heart never takes place in healthy tissue, except in calcium metastasis where it involves the endocardium only.

#### THEORIES ON CALCIFICATION OF THE HEART

All textbooks on pathology agree that calcification of the heart is a very rare condition. Aschoff<sup>44</sup> and Kaufmann<sup>45</sup> add that the calcification process, as a rule, is preceded by a regressive metamorphosis of the heart muscle fibers, except possibly where the process is part of a general calcium metastasis when it is associated with calcium deposits in the kidneys, stomach, lung and sometimes in ulcer of the liver. Adam<sup>46</sup> doubts whether calcification ever takes place in living tissue. He is inclined to believe that it occurs only in dead tissue. Even in cases of calcium metastasis, where calcium apparently is deposited in living tissue, careful

40 Diemer. *Ztschr f Heilk* 20 185, 1899

41 Oberndorfer. *Munchen med Wchnschr* 53 2081, 1906

42 McFarland. *J. The Pathology and Pathogenesis of Pericarditis*, J. A. M. A 37 1507 (Dec 7) 1901

43 Lucas. *Pericardial Calcification*, Brit M J 2 1404 1907

44 Aschoff. *Pathol Anatomie*, Jena, G Fischer, 2 20, 1919

45 Kaufmann. *Lehrbuch d Spez Pathol Anatomie* Berlin, G Reimer 1 35, 1911

46 Adam and Nicholls. *Principles of Pathology* Philadelphia, Lea & Febiger, 1911, 1.930, 2.154



microscopic examinations, he thinks, tend to show that the calcifying process in such instances involves not the living cellular tissue but only the inanimate, intercellular parts of the living tissue. MacCallum<sup>47</sup> does not take any definite stand. According to his opinion there are so many still unsolved questions involved in the consideration of this subject, that no definite conclusions can be reached at the present time. According to Wells,<sup>48</sup> heteroplastic calcification never occurs in normal tissue, except perhaps in metastatic calcinosis.

Special studies in connection with the subject of calcification in general have been made by Aschoff,<sup>49</sup> Lichtwitz,<sup>50</sup> Gierke,<sup>51</sup> Goldthwait,<sup>52</sup> Erlich,<sup>53</sup> Schultze<sup>54</sup> and Wells<sup>55</sup>. These authors could not solve the problem, but came to the conclusion that many points, with regard to the causative factors of pathologic calcification, still remain obscure and unexplained, and that it would be of great interest and importance to study more minutely the normal calcification process, especially to find out which elements of the cartilage take up the calcium first. Wells calls attention to the interesting feature of the daily excretion of from 4 to 5 gm of calcium carbonate by a laying hen, and to the investigations made as to the nature of the stimulus which causes a shell to be formed on a bird's egg. Here one may add the likewise interesting observation commonly made on farms that a certain injury may cause a hen to lose her ability of forming a shell around her egg, to lay eggs without a shell for a period of time, and finally to gradually regain her lost capacity of forming a calcium shell.

The nature of calcification in cases of the so-called calcium metastasis, like in the instances of Virchow,<sup>1</sup> Versé,<sup>24</sup> Leyden, Wiechert<sup>21</sup> and Roth,<sup>10</sup> has been dwelt on by Wells,<sup>55</sup> Askanazy,<sup>12</sup> Hofmeister,<sup>56</sup>

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47 MacCallum, W. G. Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1920, pp. 106 and 253.

48 Wells, H. G. Chemical Pathology, Philadelphia, W. B. Saunders Company, 1920, p. 439.

49 Aschoff. Verkalkung, *Ergebn d path* **8** 1, 1902.

50 Lichtwitz. Ueber d Bedeutung d Kolloide f d Konkrementbildung u die Verkalkung, *Deutsch med Wchnschr* **36** 704, 1910.

51 Gierke. Ueber Eisengehalt verkalkter Gewebe unter normalen u pathol Bedingungen, *Virchows Arch f path Anat* **167** 318, 1902.

52 Goldthwait, Painter, Osgood, and McCrudden. A Study of the Metabolism in Osteomalacia, *Am J Physiol* **14** 389, 1905.

53 Erlich. Eisen impregnation and Kalk impregnation i menschel Geweben, insbesondere den elastischen Fasern, *Zentralbl f path* **17** 177, 1906.

54 Schultze. Die Verkalkung, *Ergebn d allg path* **14** 707, 1910.

55 Wells, H. G. Calcification and Ossification, *Arch Int Med* **7** 721 (June) 1911, Pathological Calcification, *J M Res* **14** 491, 1906, Wells and Benson. Studies on Calcification, *J M Res* **12** 15, 1907, Wells and Mitchell. Studies on Calcification and Ossification, *J M Res* **22** 501, 1906.

56 Hofmeister. Ueber Ablagerung u Resorption v Kalksalzen i d Geweben, *Ergebn d Physiol* **10** 429, 1910.

Huebschmann<sup>57</sup> and Schmidt<sup>58</sup> They explain the calcium deposits in the kidneys, lung and stomach of such cases by the fact that in these organs acids are excreted into cavities which leave the fluids in the substances of these parts correspondingly alkaline This increase in the alkalinity of the fluids makes the calcium salts decidedly less soluble so that in instances where for some reasons the total amount of free calcium salts in the body fluids is greatly increased, calcification in these organs may take place under certain conditions Such calcifying process may possibly be aided by a nephritis which latter, according to Schmidt,<sup>58</sup> may cause blood changes which tend to diminish the solubility of the calcium salts He succeeded in such a case in demonstrating precipitation of calcium in the blood Erbe<sup>59</sup> found increased amounts of calcium in the blood in some cases of nephritis

Thorel,<sup>60</sup> in reviewing the literature on myocardial calcification, is of the opinion that the subject of calcification of the heart as well as calcium metastasis is so little cleared up that it is impossible to arrive at any definite conclusions He somewhat doubts the existence of metastatic calcosis, as does also Askanazy<sup>12</sup> and Kockel<sup>61</sup>

The question of heteroplastic bone formation in general, and of bone formation within calcified areas of the heart and arteries, as well as of other parts of the body has been made the subject of investigations by Porscharisky,<sup>62</sup> Buerger and Oppenheimer,<sup>63</sup> Harvey,<sup>64</sup> Rosenstein,<sup>65</sup> Rohmer,<sup>66</sup> Maximow<sup>67</sup> and others Of special interest are the observations made with regard to the changes which, under certain circumstances, may gradually take place within the cells constituting the calcified mass and which may slowly lead to the formation of blood vessels This tends to show that the ultimate cause of heteroplastic ossification,

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57 Huebschmann Zur Histologie d Kalkmetastase, Zentralbl f Allg Path u Path Anat **19** 737, 1908

58 Schmidt Kalkmetastase u Kalkgicht, Arb a d Path Inst Marburg, 1913

59 Erbe Ueber die Zusammensetzung d Blutes Zentralbl f klin med **1**·441, 1903

60 Thorel Pathol Krauslauforgane Ergebn d Pathol **2** 284, 1910

61 Kockel Deutsch Arch f klin med **64** 332, 1899

62 Porscharisky Ueber heteroplastische Knochenneubildung Beitr z path Anat u z allg Path **38** 135, 1905

63 Buerger and Oppenheimer Bone Formation in Sclerotic Arteries, J Exper Med **10** 354, 1908

64 Harvey Experimental Bone formation in Arteries, J. M Res **17**·25 1907

65 Rosenstein Ueber Knochen und Knorpelbildung i Herzklappen, Virchows Arch f path Anat **162** 100, 1900

66 Rohmer Ueber Knochenbildung i verkalkten endokarditischen u endoarterit Herden, Virchows Arch f Anat **166**·13, 1901

67 Maximow Ueber experimentelle Erzeugung v Knochenmarkgewebe, Anat Anz **28** 609 1906

and probably also of heteroplastic calcification, will have to be looked for within the cell itself

Very much has been accomplished toward the final solutions of these various problems by the results of experimentally produced calcification in normal animals as done by Kossa,<sup>68</sup> Wells,<sup>55</sup> Tanaka,<sup>69</sup> Katase<sup>70</sup> and Albrecht<sup>71</sup> The latter author succeeded in obtaining calcification of heart muscle fibers in rabbits by the injection of influenza bacilli The information gained by these animal experiments may briefly be summed up thus

### RESULTS

Calcification may be produced in a normal animal by means of introduction of a sufficient amount of calcium salts, which amount is comparatively large

Calcification may take place practically in any organ, among others, in the heart

Calcium is excreted mainly by the kidneys, intestines (especially the large intestine) and bronchi

Calcification may be aided by interference with the calcium excretion and by diminution of the calcium tolerance of the cells of the individual organ

Degeneration of the tissue diminishes the calcium tolerance of its cells

The frequency of calcification in the various organs depends on the calcium tolerance of the cells and the physiologic metabolic capacity of the individual organ

Among the tissue elements which attract calcium salts, the elastic tissue fibers take the first place

Of interest in this connection also may be the experiments of Werra<sup>72</sup> He has shown that in animals temporary ligation of the renal artery for one hour may cause calcification of the petechial elements of the kidney The calcification process is completed within from six to seven days after removal of the ligation From the eighth day on the calcification begins to be gradually absorbed again, and disappears entirely within from thirty-five to forty-four days, at which time the kidney again presents a normal appearance

Calcification of the coronary vessels of the heart and of its valves may occur very early in life, as shown by Surbeck,<sup>73</sup> who reports calcification near the aortic valves and of the coronary arteries in an infant, aged 2 days, presenting diplococcus infection with fibrinous pericarditis

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68 Kossa Ueber die in Organen kuenstl erzeugte Verkalkung, Beitr z path Anat u z allg Path **29** 163, 1903

69 Tanaka Ueber die Kalkresorption und Verkalkungen, Biochem Ztschr **35** 113, 1911, **38** 285, 1912

70 Katase Experimentelle Verkalkungen am gesunden Tiere, Beitr z path Anat u z allg Path **57** 517, 1914, Experimentelle Kalkmetastase, Bern, 1916

71 Albrecht Zentralbl f allg Path u path Anat **20** 1031, 1909

72 Werra Ueber d Folgen d voruebergehenden u dauernden Verschlusses d Nierenarterie, Virchows Arch f path Anat **88** 197, 1882

73 Surbeck Ueber einen Fall v congenitaler Verkalkung m vorwiegender Beteiligung d Aorta, Zentralbl f allg Path u path Anat **28** 25, 1917

The investigations by Baeumler<sup>74</sup> show that calcification of arteries is not necessarily a senile condition, but may be produced irrespective of age, by mechanical, toxic, infectious and other influences

Wells comes to the following conclusions with regard to pathologic calcification. Retrogressive changes are for pathologic calcification, a condition *sine qua non*, except in metastatic calcification. Deposition of calcium salts in such areas of degeneration depends on (1) increased alkalinity or decreased carbon dioxide in degenerated tissues causing precipitation of the inorganic salts in the fluids seeping slowly through them, (2) utilization of the protein of the fluids by the starved tissues so completely, because of its slow passage through them, that the calcium cannot be held longer in solution, (3) formation within the degenerated area of a substance or substances having a special affinity for calcium, (4) production of a physiologic condition favoring the local absorption of salts, the least soluble salts accumulating in excess

#### SUMMARY

The material just presented shows that there still are many questions to be solved with regard to heteroplasic calcification, within the heart as well as within other parts of the body. We still do not know why it is that, given two cases of exactly the same pathologic conditions, one will present extensive calcification within the heart, while the other one will reveal none. Extensive bone destructive processes are so very frequent, and yet cases of calcium metastasis are so extremely rare. There is hardly any doubt that calcium metastasis or rather "heteroplasic calcium impregnation" really occurs. One may even be justified in stating that it forms a definite clinical entity as described above. The apparently direct taking up by the endocardium of the calcium salts in the auricles, where there are, for obvious reasons, more favorable conditions for such a process to take place than in the ventricles, is even more characteristic of "*metastatic* calcium impregnation" as it really ought to be called, than the coexisting calcification process in the lung, kidneys and stomach.

Some of the discrepancies of opinion, with regard to calcification of the heart, as met with among the authors of the cases enumerated in Table 1, could possibly be explained by the observation that some of them, it seems, have made mistakes such as could occur at similar occasions. In some instances, findings in too small a series of cases have been generalized and quite blindly set down as definite rules for the entire subject of calcification of the heart. In other instances, apparently not quite correct interpretations by the original authors have been

<sup>74</sup> Baeumler. Ist die Arteriosclerose eine Allgemeinerkrankung? Berl klin Wchnschr 42 38, 1905

indiscriminately accepted as correct by other writers, thus leading to wrong theorizing and incorrect classification, similar to the cases of Heschl and Tilp, and to a certain degree also to that of Wiechert. Furthermore the results gained by experiments in *normal* animals, have been applied, it would seem, occasionally in a somewhat unqualified manner to the human body, where the calcification process very often is the outcome of a combination of *pathologic* conditions in various organs. Especially complicating in this respect is the close interrelationship between cardiac and renal conditions, so that very often it is difficult or even impossible to hold distinctly apart the rôle played by each one of these two factors in the production of myocardial calcification.

Taking into due consideration all the points brought out by the various writers on our subject as briefly mentioned before, and making allowances for apparent slight errors made by some authors of the published cases, one is justified in arriving at the following conclusions:

#### CONCLUSIONS

Calcification of the heart, like any other pathologic calcification, may occur in two different forms: (1) *deposition* of calcium salts within the cardiac tissue, (2) *precipitation* of calcium salts directly into the endocard.

1 Deposition of calcium salts within the heart takes place only in dead or markedly deteriorated, never in healthy, tissue. The condition is not very uncommon.

The process begins with deposition of fine calcium granules, usually calcium phosphate, within the broken up heart muscle fibers. These calcium granules may gradually coalesce, forming plaques, the latter gradually involving all the elements of the heart substance.

There is no specific clinical cause for the condition, but the calcification can occur in the course of any pathologic condition which gradually leads to degeneration of cardiac muscle fibers of diffuse or localized type.

What rôle pathologic conditions of the kidneys, causing interference with calcium excretion and thereby possibly increase in the total amount of free calcium salts, may play in aiding the production of myocardial or any other pathologic calcification, has not definitely been determined yet.

The ultimate cause of pathologic calcium deposition seems to lie in the factors controlling the calcium tolerance of the cell, and in the character of physicochemical processes within the individual cells.

2 Calcium precipitation involves the endocardium only. It is an extremely rare condition, only two cases being known so far, both of which were observed in combination with the so-called calcium metastasis.

By metastatic calcification is understood the direct deposition or rather precipitation into apparently normal tissue of the overload of circulating calcium salts produced by extensive bone destructive processes within the body

The precipitated calcium salts in such cases are found in the kidneys stomach lung and occasionally in the auricles of the heart In the kidneys the calcification process involves the glomeruli and to a lesser degree also the canaliculi in the stomach the interstitial tissue of the mucosa in the lung the elastic tissue in the heart the endocardium of the left auricle to a lesser degree also of the right

Calcium metastasis could be considered a clinical entity composed of the clinical picture of the primary bone destructive lesion finally superimposed by a second clinical picture somewhat suggestive of acute rheumatism

The final causes of calcium metastasis are not definitely known but it is fair to assume that the main causative factors consist of the oversaturation of the circulation with calcium salts associated later on with a breakdown of the mechanism normally provided for the excretion of calcium salts followed finally by precipitation of the calcium overload in the places mentioned in the foregoing

3 Roentgenologically calcification of the heart may be demonstrated *intra vitam* if extensive enough In such instances one may even succeed in differentiating it from pericardial calcification

Small calcified foci within the heart cannot be demonstrated by the roentgen ray during lifetime.

Small fine solitary calcified foci within the heart wall may be sometimes overlooked at necropsy. This may be avoided to a large extent by taking roentgenograms of the removed necropsy specimen whereby even very fine calcified areas are clearly demonstrated and localized

Such necropsy radiographic work if carried on systematically will show that myocardial calcification is not so very rare as is generally believed

The use of the roentgen ray should be considered a very important aid for the pathologist in his search for small calcified foci and for other changes which cause radiographically sufficient differentiation of tissue densities

# THE RATIONAL USE OF DUODENAL DRAINAGE

AN ATTEMPT TO ESTABLISH A CONSERVATIVE ESTIMATE OF THE  
VALUE OF THIS PROCEDURE IN THE DIAGNOSIS  
OF BILIARY TRACT PATHOLOGY \*

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Few laboratory methods introduced in recent years have attracted such widespread attention throughout medical circles as the so-called Meltzer-Lyon method of biliary drainage. The literature for the last three years includes at least fifty articles on the subject, and the method has been widely used throughout this country, as well as in England and on the Continent. A review of the literature would be of little value, as many of the articles are merely clinical impressions, and are not based on careful investigative work. It may be said, however, that the various articles fall roughly into two groups, those upholding, and those denying the value of duodenal drainage. According to Lyon,<sup>1</sup> Smithies, Karshner and Oleson,<sup>2</sup> White,<sup>3</sup> and others, the method is of great value in the diagnosis and treatment of practically all kinds of biliary tract pathologic changes. Einhorn,<sup>4</sup> Alvarez,<sup>5</sup> Cutler and Newton,<sup>6</sup> and others, on the other hand, believe that the method is of little or no real value. The conclusions of each of these groups are largely based on rather indifferently controlled clinical studies. In addition, there is a third group of men who have confined their comment largely to the results of animal experimentation. The work of this group

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1 Lyon, B. B. V. Diagnosis and Treatment of Diseases of the Gallbladder and Biliary Ducts, *J. A. M. A.* **73** 980 (Sept. 27) 1919.

2 Smithies, F., Karshner, C. F., and Oleson, R. B. Nonsurgical Drainage of the Biliary Tract, *J. A. M. A.* **77** 2036 (Dec. 24) 1921.

3 White, F. W. The Value of Medical Biliary Drainage in Diagnosis and Treatment of Diseases of the Gallbladder and Bile Ducts, *Boston M. & S. J.* **186** 206 (Feb. 16) 1922.

4 Einhorn, M. Action of Various Salts and Other Substances on the Liver After Their Introduction into the Duodenum, *New York M. J.* **114** 262 (Sept. 7) 1921.

5 Alvarez, W. C. Diagnosis and Treatment of Gallbladder Disease with Special Reference to the Meltzer-Lyon Test, *M. Clin. N. Amer.* **6** 213 (Sept.) 1922.

6 Cutler, E. C., and Newton, F. C. Some Experiences with the "Meltzer-Lyon" Test in Gallbladder Disease, *Surg., Gynec. & Obst.* **35** 146 (Aug.) 1922.

includes papers by Auster and Crohn,<sup>7</sup> Friedenwald Martindale and Kearney,<sup>8</sup> Frazer,<sup>9</sup> Diamond,<sup>10</sup> McWhorter<sup>11</sup> and a few other authors. A careful survey of the literature seems to indicate that as yet a conservative and fair estimate of the value of duodenal drainage has not been made.

Unquestionably the early, rather extravagant claims for the method, as a means of diagnosis and treatment have not been fulfilled. It is also unfortunately true that much of the criticism and pessimism with which the subject is now viewed is due to the claims that have been made by some enthusiasts as regards the efficacy of treatment by duodenal drainage. The undoubted psychologic effect produced by such treatment has undoubtedly been overlooked or not mentioned by many. On the other hand the somewhat unequivocal stand of Alvarez<sup>5</sup> and other authors that the method is without any value, seems equally unjustifiable. It is the purpose of this paper to present evidence that duodenal drainage is justifiable in a selected group of cases and that in this group it is of definite diagnostic or therapeutic value.

Before discussing the therapeutic value of duodenal drainage, I wish to comment briefly on the experimental evidence at hand that bears on the physiology of the gallbladder and the sphincter of Oddi. According to the early experiments of Doyon,<sup>12</sup> Bambridge and Dale,<sup>13</sup> Freese<sup>14</sup> and Okada<sup>15</sup> the gallbladder is capable of producing muscular contractions, the frequency and intensity of which may be modified by various stimuli. The introduction into the duodenum, for instance, of acid chyme, increases the strength and frequency of such contractions. Other stimuli, such as morphin, were observed to produce an opposite result.

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7 Auster, L. S. and Crohn, B. B. Notes on Study of the Physiology of the Gallbladder, *Am J M Sc* **164** 345 (Sept.) 1922.

8 Friedenwald, I., Martindale, J. W., and Kearney, F. X. Animal Experiments on Certain Phases of the Lyon-Meltzer Method of Biliary Drainage. *J Metab Res* **2** 349 (Sept.) 1922.

9 Frazer, E. B. The Effect of Magnesium Sulphate on the Secretion of Bile, *J A M A* **79** 1594 (Nov. 4) 1922.

10 Diamond, J. S. An Experimental Study of the Meltzer-Lyon Test, with Comment on the Physiology of the Gallbladder and Sphincter Vateri, *Am J M Sc* **166** 894 (Dec.) 1923.

11 McWhorter, G. L. The Surgical Significance of the Common Bile Duct Sphincter, *Surg, Gynec & Obst* **32** 124 (Feb.) 1921.

12 Doyon, M. Contribution a l'etude de la contractilité des voies biliaires, *Arch de Physiol norm et path* **25** 678, 1893.

13 Bambridge, F. A., and Dale, H. H. The Contractile Mechanism of the Gallbladder and Its Extrinsic Nervous Control, *J Physiol* **33** 138 1905 and 1906.

14 Freese, J. A. The Force of Contraction of the Gallbladder and the Course of Its Motor and Inhibitory Nerve Fibers, *Bull Johns Hopkins Hosp* **16** 235, 1905.

15 Okada, S. Contractile Movements of the Gallbladder. *J Physiol* **50** 42, 1915.



The exact mechanism controlling the activity of the gallbladder has been proved to depend on two sets of nerve fibers, one motor, and the other inhibitory. Later Meltzer<sup>16</sup> conceived the idea of a coordinated nervous control of the sphincter of Oddi and the gallbladder musculature, of such a nature that stimuli causing a relaxation of the sphincter simultaneously caused a contraction of the gallbladder, and vice versa. Although never proved experimentally, this idea of a contrary innervation in the biliary system was rather generally accepted, and at present forms the basis of the so-called Meltzer-Lyon method of nonsurgical biliary drainage. The method was based on a theoretical suggestion made by Meltzer that the instillation of a solution of magnesium sulphate into the duodenum would cause a relaxation of the sphincter of the common bile duct, and a simultaneous contraction of the gallbladder. Such a theory, if true, would quite logically afford a rational means of studying and treating gallbladder pathology, and the widespread acceptance of Lyon's original work is testimony to the apparent rationality of the hypothesis. Recent experimental work, however, points against the soundness of Meltzer's, and subsequently Lyon's, theory of "contrary innervation," and to a rather large degree invalidates Lyon's claims and methods. A review of Bainbridge and Dale's, and Okada's original work indicates that, while gallbladder contraction can be demonstrated, such contractions were so slight as to require very delicate and highly magnified methods to show clearly their existence. Furthermore, it must be recalled that a large majority of the gallbladders investigated by Lyon's technic are diseased organs, with thickened and fibrosed walls. It appears inconceivable that a chemical stimulus applied to the duodenal mucosa can produce contractions in gallbladders, diseased or otherwise, of sufficient magnitude to empty the organ. The work of Auster and Crohn<sup>7</sup> on animals suggests that the action of magnesium sulphate, when introduced into the duodenum, does not cause a contraction of the gallbladder. Clinical observations, following the use of intraduodenal magnesium sulphate during laparotomy, have given conflicting results. The majority of observers agree that under such conditions no contraction or emptying of the gallbladder occurs. All such evidence is, however, open to the criticism that normal nerve reactions were abolished by the anesthesia, and is therefore of little value. That magnesium sulphate does relax the duodenum in the majority of instances, when introduced therein, is definitely proved by the work of Frazer<sup>9</sup> on animals. This investigator produced evidence

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16 Meltzer, S. J. The Disturbance of the Law of Contrary Innervation as a Pathogenic Factor in the Diseases of the Bile Ducts and the Gallbladder, *Am J M Sc* **153** 469 (April) 1917

that the action of the drug is purely local, Einhorn,<sup>1</sup> Dunn<sup>17</sup> and others to the contrary notwithstanding. Similar experimental results were obtained by Friedenwald, Maitindale and Kearney<sup>8</sup> on dogs. These workers not only obtained no evidence of central action following the use of the drug, but were also unable to demonstrate any contraction of the gallbladder. Recent work by Diamond<sup>10</sup> appears, at last, to produce unanswerable proof of the inaccuracy of Lyon's original hypotheses. In Diamond's experiments on dogs with duodenal fistula, repeated intraduodenal injections of a solution of magnesium sulphate, in ambulatory animals, failed to show expulsion into the duodenum of carmin previously introduced into the gallbladder. These experiments covered a reasonable period of time (from six to eight days), and during the entire period no macroscopic evidence of carmin appearing in the duodenum could be obtained. Occasionally, rare microscopic particles of the dye were seen, but no evidence of gross gallbladder contractions could be elicited. In the presence of such carefully controlled experiments, and especially in view of the notable absence of any experimental work in favor of Lyon's theories, it would seem illogical to accept longer the hypothesis that there exists a crossed innervation between the sphincter of Oddi and the gallbladder musculature, or that magnesium sulphate, peptones, hydrochloric acid, or other substances, when introduced into the duodenum, do more than cause a local relaxation of the duodenal wall, and with it the muscle fibers of the sphincter of Oddi.

With regard to the value of the sequence of "A," "B" and "C" biles, the before mentioned evidence would destroy the possibility of real significance attaching to color changes in the bile flowing into the duodenum. Surely, if gallbladder contractions are not to be expected following magnesium sulphate lavage, so-called "B" bile loses its significance. Clinically, it has been shown that "B" bile can be observed, even in cases of obstructed cystic duct, or in the absence of the gallbladder.<sup>17</sup> I have frequently observed such a phenomenon, and have proved the presence of increased bile pigments by spectroscopic analysis. Consideration of the cases in which "B" bile has been noted, in the absence of the gallbladder, indicates that in these cases there was an associated involvement of the entire biliary tract, with resulting liver disturbance. In a previous article<sup>18</sup> I have already shown that under such conditions of hepatic disturbance the liver bile is practically always very dark, due to increased pigment content. What, then, is the logical explanation of the so-called "gallbladder" or "B" fraction? A reasonable explanation

17 Dunn, A. D., and Connell, K. Report of a Case of Hepatoduodenostomy, *J. A. M. A.* **77** 1093 (Oct.) 1921.

18 Jones, C. M. Blood Pigment Metabolism and Its Relation to Liver Function, *Arch. Int. Med.* **29** 643 (May) 1922.

would seem to be that the fraction of duodenal contents containing the highest concentration of bile pigments is merely that portion collected during the greatest flow of bile into the duodenum, *i. e.*, during the greatest relaxation of the sphincter of Oddi, following the use of magnesium sulphate. As soon as the relaxation of the duodenum and sphincter diminishes, the flow of bile also diminishes and the amount of bile pigment per unit volume of duodenal contents is correspondingly lowered. Subsequent fractions are, therefore, lighter in color, although repeated instillations of magnesium sulphate will produce continued increases in pigment. Such an explanation is simple, it does not depend on unproven hypotheses, and incidentally deprives the method of much of its picturesque appeal. That the duodenal contents may contain small amounts of gallbladder bile, however, is probable, and is suggested by the finding of microscopic amounts of carmin in Diamond's experiments, which have already been alluded to. Such small amounts of gallbladder bile can undoubtedly be accounted for by passive siphonage during an increased flow of liver bile.

From experimental and clinical evidence, therefore, it seems justifiable to conclude that the diagnosis and treatment of gallbladder pathologic changes, based on the collection "gallbladder" bile, is extremely illogical and unwarranted. Of what use, then, is duodenal lavage, either in the diagnosis or treatment of biliary tract pathologic changes? In spite of the before mentioned adverse criticism, which I think is warranted, I believe that the method can be intelligently used in selected cases to distinct advantage, both therapeutically and as a diagnostic measure.

Attempts to treat chronic disease of the gallbladder by duodenal lavage with instillations of magnesium sulphate, or other solutions, seem to be illogical for reasons before mentioned. Gallbladder drainage by such means must be, at most, microscopic in amount. In addition, it is well to recall that the pathologic changes of chronic cholecystitis lies in the walls of the organ, and not in the mucosa or in the bile contained in the viscus. With such a pathologic picture the hope of curing such a process by ineffective gallbladder "drainage" appears remote. In cases of acute cholecystitis, in which the organ is presumably under increased tension, prolonged complete relaxation of the sphincter of the common bile duct, with a resulting free flow of bile, may conceivably aid in a passive partial evacuation of the gallbladder with slight relief of symptoms. Cholelithiasis need only be mentioned as a condition not amenable to any forms of medical therapy, except for symptomatic relief. The psychologic element of bile drainage must be emphasized, and undoubtedly accounts for many "cures" of "chronic cholecystitis"—a disease at best presenting an extremely difficult diagnostic problem.

A similar criticism might be justified, in passing, of the relief following duodenal drainage, claimed in such diseases as diabetes mellitus, hemolytic jaundice, etc

One type of disease of the biliary tract can be successfully treated by this method. Sufficient clinical evidence has been presented to warrant the conclusion that infectious (catarrhal) jaundice can be relieved, and the course of the disease shortened by frequent duodenal lavage. The procedure is logical in such cases, inasmuch as the local effect of the magnesium sulphate solution allows a relaxation of the sphincter of Oddi, with a resulting flow of bile. As the pathologic changes of infectious jaundice lies primarily in the liver, biliary drainage offers a feasible method of treatment. Observations by Lyon<sup>19</sup> and others have already indicated the value of such treatment, and a recent communication by Jones and Minot<sup>20</sup> shows graphically the probable results of duodenal drainage in cases of infectious jaundice. It seems probable, by analogy, that a similar procedure in cases of arsphenamin jaundice is warranted. Observations on several cases indicate that favorable results may be expected.

From the nature of the pathologic changes of other diseases of the biliary system, duodenal drainage in cirrhosis, cancer, etc., would hardly be expected to be a rational form of therapy.

From the point of view of exact diagnosis, the value of duodenal analysis is also limited. A study of the bacteriology of the duodenal contents is now generally considered to be of little value. Contamination cannot be excluded, even by the most rigid technic, and positive cultures, even when obtained, rarely give an indication of the location or of the type of the existing pathologic changes. One exception must be made to this rather general statement. The detection of typhoid carriers can readily be made by culture of the duodenal contents, but no special precautions have been found necessary, in my experience, beyond a sterile duodenal tube.

For diagnostic purposes there remains, then, the examination of the duodenal contents for (1) bile pigments, (2) cellular elements and (3) crystalline elements.

Although the attempts to divide the duodenal contents into "A," "B" and "C" fractions are of little or no value, for reasons already given, estimations of the amounts and types of bile pigments present in a given specimen are of some importance. It has been shown by numerous observers that the concentration of the bile pigments is abnormally high

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19 Lyon, B. B. V. The Treatment of Catarrhal Jaundice by a Rational Direct and Effective Method, *Am J M Sc* **159** 503 (April) 1920.

20 Jones, C. M., and Minot, G. R. Infectious (Catarrhal) Jaundice, an Attempt to Establish a Clinical Entity, *Boston M & S J* **189** 531 (Oct 18) 1923.

in cases associated with increased blood destruction. The writer has confirmed these findings, and in addition, has shown that an increase of the bile pigments in the duodenal contents occurs in various types of liver disturbance.<sup>18</sup> Inspection of the results obtained in approximately 600 analyses has shown that the pigment content of the bile is increased in (1) pernicious anemia, hemolytic jaundice, malaria, hemolytic streptococcus septicemias, Banti's disease, paroxysmal hemoglobinuria, certain cases of polycythemia, acute lead poisoning, and (2) in certain phases of infectious (catarrhal) jaundice, diarsenol jaundice, some of the cirrheses, cancer of the liver, and many cases of chronic cholecystitis and cholelithiasis, chronic passive congestion of the liver, and other types of liver disturbance, including the majority of cases of diabetes mellitus. The high bile pigment concentration observed in cases of chronic cholecystitis and cholelithiasis I believe to be due, not to stasis of bile in the gallbladder, but probably to an associated disturbance of the liver, a common occurrence in chronic gallbladder disease. Examination has also shown that in cases associated with abnormal blood destruction, or with alteration of liver function, not only are the total bile pigments increased in amount in the duodenal contents, but the presence of abnormal proportions of the various pigments also occurs. Normally, the bile contains bilirubin and urobilin and occasionally small traces of urobilinogen. In abnormal blood destruction, and in cases of marked liver disturbance, the proportion of urobilin or urobilinogen increases strikingly, and rarely one finds the rare pigment cholecyanin. A detailed discussion on the significance of changes in the bile pigments is to be found in articles already published.<sup>21</sup> Briefly, then, an abnormal pigment content of the bile may indicate the existence of one of several disease conditions, but is not conclusive evidence of the presence of any single disease.

Turbidity and increased viscosity of the duodenal contents have been frequently mentioned as of diagnostic significance. They may be due to many causes besides biliary tract pathologic changes, and may be entirely wanting in the presence of marked biliary disease. They are of no diagnostic importance.

Microscopic examination alone seems to be of practical value in the diagnosis of biliary disease by means of duodenal drainage. Such a statement is partly in harmony with Lyon's original claims, but is distinctly contrary to the conclusions of numerous investigators, including Alvarez,<sup>5</sup> Cutler and Newton<sup>6</sup> and others. In my experience, a careful examination of a large number of sediments of duodenal contents has shown that certain features may be of diagnostic significance.

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21 Jones, C. M. Alterations in Liver Function and in the External Secretory Activity of the Pancreas in Diabetes Mellitus. A Preliminary Report. Boston M. & S. J. **189** 851 (Nov. 29) 1923, also Footnotes 18 and 20.

Bile-stained leukocytes and epithelial cells in any quantity are not found in normal patients. They do occur in the presence of an inflammatory condition involving the biliary tract, although it is not possible to determine from the type of cell found in the duodenal sediment the exact level of the inflammatory process. In infectious (catarrhal) jaundice there is a large amount of such bile-stained cellular material during the early stages of the disease. In acute cholecystitis similar findings may be obtained, but are not constant, and other clinical and laboratory findings are of much greater diagnostic value. The exact information to be derived from a study of the cellular elements of the duodenal contents may be said, therefore, to be largely confirmatory. Too much reliance cannot be placed on the mere finding of abnormal amounts of bile-stained cells, although in most cases such findings indicate biliary tract inflammation. The significance of such findings will receive further comment.

There remains but to mention the finding of abnormal crystalline elements in the duodenal contents. In my experience, based on the analysis of a large number of cases, the finding of abnormal amounts of cholesterol, bilirubin or calcium bilirubinate has been of real diagnostic value. As already indicated, the attempted segregation of different samples of bile and the localization therefrom of biliary pathologic changes, by attention to color, bacteriology, or cellular elements, has not proved logical or susceptible of proof. On the other hand, careful examination of the following results would seem to indicate that the finding of abnormal crystalline elements in the duodenal contents is of diagnostic significance, and in itself warrants the use of a time consuming and unpleasant laboratory method.

#### CLINICAL MATERIAL

The clinical material forming the basis of this investigation consists of three groups of cases, with a total of 274 individual patients. The first group, the findings in which are shown in Table 1, consists of fifteen normal controls. The members of the group were normal medical students and members of the laboratory staff. The second group is comprised of 202 patients, taken from the medical and surgical wards of the Massachusetts General Hospital. As shown in Table 2, the patients included in this group were suffering from various types of disease, in all, twenty-seven different diseases were diagnosed. This group, therefore, may be considered as a group of pathologic controls. The third group of cases (Tables 3, 4 and 5) was made up of fifty-seven patients with a definite diagnosis of cholelithiasis. Of the fifty-seven patients in this series, forty-two were operated on and were proved to have had gallstones. The remaining fifteen cases were patients in which the diagnosis was perfectly obvious, and was agreed on by both medical

and surgical consultants. Operation was not performed on these patients because of their general condition, or because of their unwillingness to undergo laparotomy.

#### METHOD

The following description of the method employed in collecting and examining the duodenal contents will be seen to differ in certain essential details from that described by Lyon and others. Following the introduction of the duodenal tube into the duodenum, the position of the tip was carefully checked by fluoroscope. Other means of determining the exact position of the tube have been found to be inaccurate, and often misleading. An instillation of 60 c.c. of warm 33 per cent magnesium sulphate solution was then made into the duodenum, and immediately thereafter passive siphonage was begun. No suction apparatus was employed. As soon as a flow of bile was established, the duodenal contents were collected in brown glass bottles, and siphonage continued for one-half hour. The tube was then withdrawn, and the duodenal contents well mixed and centrifuged at once at high speed for fifteen minutes. This high speed centrifugalization is extremely important, and failure to obtain a sediment in this manner accounts for many of the failures to get consistent and satisfactory results (examination of specimens "fished" out of the duodenal contents cannot be expected to yield consistent results). The sediment obtained by high speed centrifuging was carefully drawn from the centrifuge tubes, after decanting the supernatant fluid, and examined microscopically. Note was made of clumps of cholesterol crystals, bilirubin or calcium bilirubin, and abnormal amounts of bile-stained cellular elements. At the same time, a portion of the duodenal contents was examined spectroscopically for the concentration and types of bile pigments. Although probably not of any absolute diagnostic significance, the bile pigment estimations, made during the course of this investigation, are included in the accompanying tables to indicate the type of pigment findings in the different diseases studied. The method of pigment estimation has been frequently described, and is briefly as follows:

To 10 c.c. of duodenal contents add an equal amount of a saturated alcoholic solution of zinc acetate. This is shaken and filtered, and to 10 c.c. of the filtrate is added 1 c.c. of Erlich's reagent. This solution is allowed to stand in the dark for fifteen minutes, and is then examined spectroscopically for the presence of bilirubin, urobilin and urobilinogen. The number of dilutions with 95 per cent alcohol necessary to remove the characteristic absorption band of a given pigment is taken as the relative amount of that pigment in a given specimen. The absorption bands of urobilin and urobilinogen are absolutely characteristic. Although it is said that bilirubin gives no characteristic shadow in the spectrum, I have found that pure solutions of this pigment give a distinct characteristic shadow in the blue-violet end of the spectrum. As the concentration of this pigment increases, the shadow involves the blue-green, and even the yellow-green. In such instances the shadow includes the band made by the urobilin present, and renders it impossible to estimate the latter pigment.

In this even the original sample, after being treated with zinc acetate and Erlich's reagent, is split in two portions. One specimen is examined for the presence of bilirubin and urobilinogen, and the dilutions estimated. The second fraction is treated with an equal amount of a 10 per cent solution of calcium chlorid. The addition of the calcium precipitates sufficient bilirubin to permit the estimation of the urobilin present. In normal persons the normal pigment concentrations have been found to be bilirubin, from 60 to 150 dilutions, urobilin, from 4 to 12 dilutions, urobilinogen, from 0 to 4 dilutions. At the time this investigation was commenced, attempts to estimate the urobilin content were unsatisfactory, and, as a result, many of the cases included in the tables have no figure for urobilin.

#### LABORATORY DATA

The results of the findings made in the various cases studied during the course of this investigation are given in tabulated form.

#### NORMAL CONTROLS

Table 1 needs no explanation. The normal controls (fifteen) all showed negative sediments and normal bile pigment concentration in the duodenal contents.

TABLE 1—*Duodenal Findings in Normal Controls*

Number of Cases 15	History Negative	Physical Examination Negative	Bile Pigments Average, 87 dilutions	Sediment Negative
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#### FINDINGS IN TWO HUNDRED AND TWO PATHOLOGIC CONTROLS

The findings made in the group of pathologic controls (Table 2) require comment. Of the 202 cases of patients with twenty-seven different diseases, 126, or approximately 62 per cent, showed negative sediments. The remaining 38 per cent, or seventy-six patients, showed some abnormality of duodenal sediment either cellular or crystalline in nature. It is to be noted, however, that in eighteen instances these abnormalities consisted only of very rare cellular or crystalline elements. Of the seventy-six cases with abnormal sediments, sixty-seven were in patients with definite or probable biliary tract pathology, and were so noted in the table. Seven had diabetes mellitus and probable cholelithiasis. Twenty-three had infectious (catarrhal) jaundice, and showed the findings elsewhere described as characteristic of that disease. The remaining ten patients with this disease were examined at a period when abnormal sediment findings were not to be expected. Nine patients with abnormal sediments had chronic cholecystitis, although twelve others with this disease showed no abnormality. Out of twenty-two patients with liver disease, fifteen showed abnormal sediments. Two out of six patients with cancer of the pancreas showed abnormalities, and these two patients were jaundiced, and showed definite involve-



ment of the biliary system Two patients with portal thrombosis, one patient with typhoid fever with right upper quadrant pain and tenderness, one patient with duodenal ulcer and gallbladder adhesions (proved at operation), and one patient with chronic biliary tract disease with

TABLE 2—Findings in Two Hundred and Two Pathologic Controls

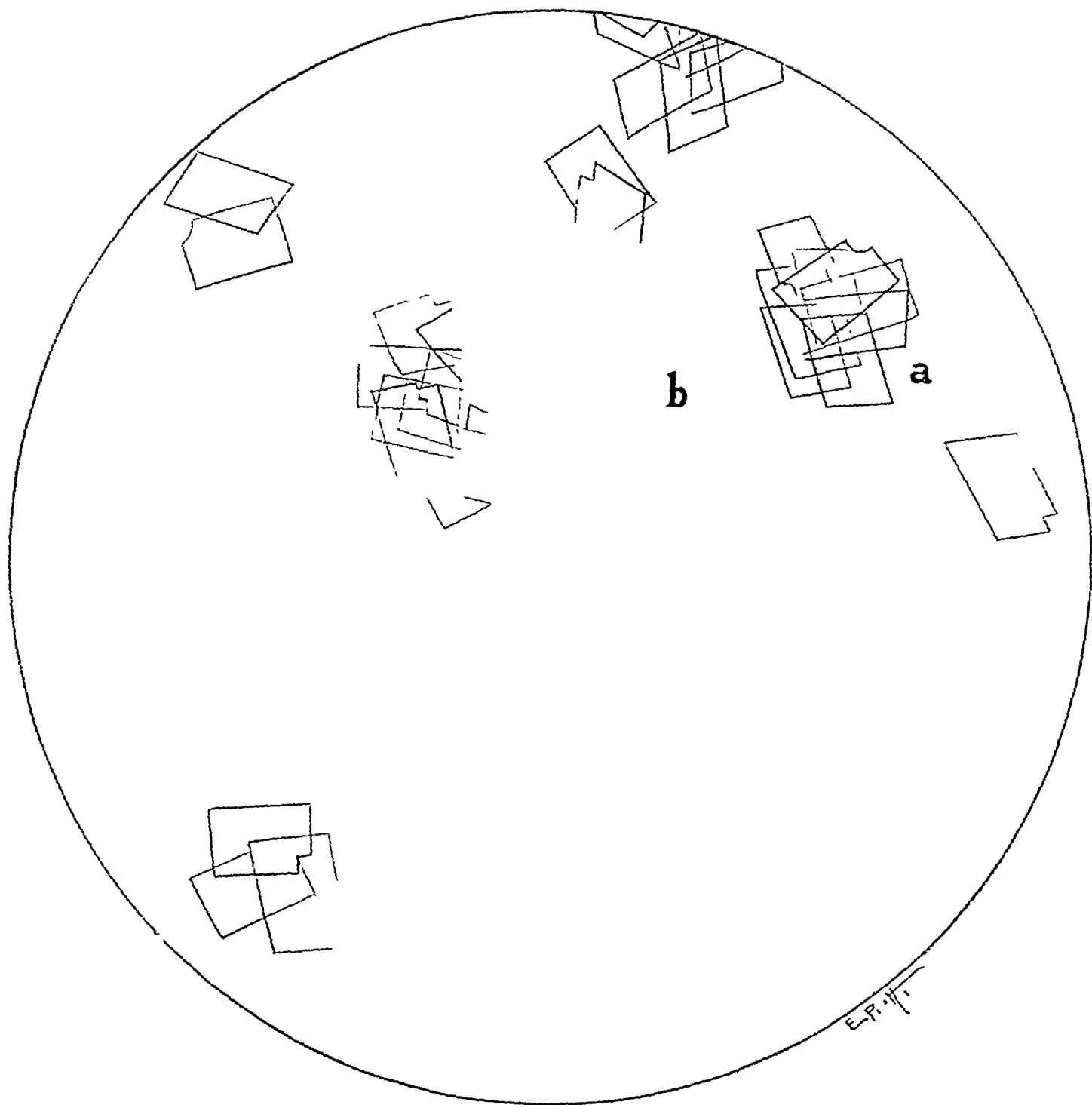
Clinical Diagnosis	No Cases	Sediment Findings					High Bile Pigments
		Negative	Abnormal	Bile-stained Cells	Cholesterol Crystals	Bile Pigment Crystals	
Diabetes mellitus (7* cases with probable gallstones)	63	52	11	7*	5	6	51
Infectious (catarrhal) jaundice*	33	10	23	13	2 (rare)	11	16
Chronic cholecystitis*	21	12	9	6	1 (4 rare)	8	7
Cirrhosis of liver (syphilitic)*	2	0	2	0	0	2	0
Cirrhosis of liver (alcoholic)*	3	3	0	0	0	0	1
Cirrhosis of liver (infectious)*	5	1	4	4	1 (rare)	0	1
Chronic hepatitis*	8	1	7	4	3 (rare) (2 rare)	4	1
Carcinoma of liver*	3	2	1	0	0	1	2
Portal thrombosis*	2	0	2	2	2	2	2
Banti's disease*	1	0	1	1	1 (rare)	0	1
Cancer of pancreas (5* cases with jaundice)	6	4	2	2	0	1	1
Acute pancreatitis†	1	0	1	0	0	1	1
Hemolytic jaundice†	2	0	2	2	0	2	2
Pernicious anemia†	9	6	3	0	2 (rare)	1	5
Typhoid (1* with right upper quadrant pain)	3	2	1	0	1	0	0
Visceroptosis and neurosis	10	8	2	1 (rare)	0	1	1
Peptic ulcer (1* case with gallbladder adhesions)	9	7	2	1	0 (rare)	2	0
Chronic appendicitis	1	0	1	1	0	0	0
Ruptured appendix	1	1	0	0	0	0	0
Lead poisoning	3	3	0	0	0	0	1
Hemochromatosis	3	3	0	0	0	0	0
Chronic arthritis	2	2	0	0	0	0	0
Postoperative adhesions (1* old gallbladder operation)	3	2	1*	1	0	0	0
Chronic purpura hemorrhagica	2	2	0	0	0	0	1
Polycythemia vera	1	1	0	0	0	0	0
Arteriosclerosis	1	1	0	0	0	0	0
Malaria	1	1	0	0	0	0	1
Bilharziasis‡	1	1	0	0	0	0	0
No pathology at operation	2	1	1	1	1	1	0
	202	126	76	46	19	43	96
1 Total number abnormal sediments in 202 cases					76		37.5
2 Total number cases with abnormal sediments and undoubted biliary tract pathology					67		33.3
3 Total number cases with marked abnormalities of sediment					53		26.7
4 Total number cases with rare abnormalities of sediment					18		9.0
5 Total number cases with unexplained abnormality of sediment					9		4.5
6 Total number cases with rare abnormalities of sediment					18		9.0
7 Total number cases with abnormal cholesterol sediment and no biliary tract pathology proven					1		0.5

\* Cases with undoubted liver or gallbladder pathology.

† Cases with probable functional disturbance of liver or bile tract.

‡ Bilharzia eggs found in duodenal sediment.

previous cholecystectomy and postoperative adhesions (found at the second operation), all showed abnormal duodenal sediments. Of the six remaining patients with probable biliary tract involvement, three had pernicious anemia, two had hemolytic jaundice, and one had acute hemorrhagic pancreatitis (examined following operation). Pernicious



Typical duodenal sediment in cholelithiasis    *a*, cholesterol crystals, *b*, bile pigment crystals



anemia is well known for the abnormal character of bile associated with the disease, and it is not surprising to have found evidences of occasional precipitated crystalline elements in these cases. Cases of hemolytic jaundice always show an abnormally high concentration of the bile pigments in the duodenal contents, and it is known that about two-thirds of all patients with this disease have pigment stones in the gallbladder or bile ducts. The findings in the two patients examined were, therefore, to be expected. Acute hemorrhagic pancreatitis, because of its close anatomic relation to the biliary tract, might well be expected to involve at least the larger bile ducts.

Thus, out of seventy-six patients showing abnormal duodenal sediments, sixty-seven can be shown to have had involvement of some portion of the biliary system. It is to be observed that of these sixty-seven abnormal sediments, forty-three showed abnormal amounts of bile-stained epithelium and leukocytes, forty showed abnormal amounts of precipitated bile pigment crystals, and only eighteen showed cholesterol crystals. Of the forty patients showing abnormal amounts of bile pigment crystals seven showed only "rare" traces, which probably had best be disregarded. Of the remaining thirty-three patients, six were presumably cases of cholelithiasis, and twenty-four of the patients showed marked liver involvement.

Of the eighteen patients showing cholesterol crystals in the duodenal sediment, nine showed only very rare crystals, and may also be disregarded. Of the remaining nine patients, five were probable cases of cholelithiasis, two were probable cases of cholecystitis, and two were cases of portal thrombosis. One patient at operation showed no demonstrable pathologic changes.

Of the forty-six patients showing abnormal amounts of bile-stained cells, forty-three showed biliary tract involvement.

Of the 202 patients, therefore, only seventy-six showed any abnormality of sediment, and of these, only nine could not be accounted for on the basis of biliary tract pathologic change. Thus, less than 5 per cent of the cases in this group presented unexplained sediment abnormalities.

It would seem logical, therefore, to assume that duodenal sediments containing abnormal amounts of bile-stained cells, bile pigment crystals, or cholesterol crystals, usually are associated with biliary tract pathologic changes. It is equally logical to conclude, however, that such findings do not in themselves give any indication of the exact locus of such pathologic changes. Abnormal sediments were found in this group in at least seventeen different conditions, and were not characteristic of any single disease entity with the exception of the findings made on patients with diabetes mellitus and probable coexisting cholelithiasis.

Several incidental findings made during the study of this group of patients are of interest. In three patients, *Lambha intestinalis* were observed in the duodenal contents. Similar findings have been reported by others, and in these patients the finding of these parasites was of no clinical importance. One of the three typhoid patients had the original infection many years prior to examination and was being studied as a carrier. Although no unusual precautions were used, except using a sterile duodenal tube and sterile culture tubes, there was no difficulty in obtaining positive cultures of typhoid bacilli. A second typhoid carrier was similarly proved in one of the patients with cholelithiasis included in Table 4. This second patient came to operation, and, following cholecystectomy, failed to show typhoid bacilli on subsequent examinations. The findings in the patient with bilharziasis are of rather

TABLE 3—Findings in Fifty-Seven Cases of Cholelithiasis

	Unoperated Cases		Operated Cases	
	Number	Per Cent	Number	Per Cent
Number of cases	15		42	
Abnormal sediment	15	100.0	42	100.0
Cholesterol	1)	6.7	3)	7.2
Bilirubin	8	53.3	24	57.0
Cholesterol and bilirubin	6)	40.0	14)	33.0
Bile-stained cells	5	33.3	16	38.0
Abnormal bile pigments	8	53.3	21	50.0
History typical for gallstones	15	100.0	28	66.6
History questionable for gallstones	0	0.0	5	12.0
History misleading for gallstones	0	0.0	6	14.3
History negative for gallstones	0	0.0	3	7.1
Physical examination positive	11	73.3	21	50.0
Physical examination questionable	3	20.0	10	24.0
Physical examination misleading	0	0.0	2	4.7
Physical examination negative	1	6.7	9	21.4
Roentgen ray taken	13	86.6	34	81.0
Roentgen ray positive for gallstones	1	6.6	2	4.7
Roentgen ray suggests gallbladder pathology	6	40.0	13	31.0
Roentgen ray negative	6	40.0	19	45.0

unusual interest. This patient was examined on several occasions, and *Schistosoma hematobium* eggs were easily found in the duodenal contents as well as in the urine. They subsequently disappeared after an extensive course of treatment. I believe this patient is the only case on record in which schistosoma eggs have been found in the duodenal contents.

## FINDINGS IN FIFTY-SEVEN CASES OF CHOLELITHIASIS

In rather definite contrast to the above findings are the results obtained in studying fifty-seven cases of cholelithiasis. These cases were not selected, but were taken indiscriminately from the medical and surgical wards of the hospital. A number of the patients had histories of physical findings that were atypical of gallstones, or else were absolutely misleading. Such patients were examined at the request of the medical or surgical service involved. For the sake of convenience

the patients are tabulated in two groups (1) those patients coming to operation, and (2) those not operated on. Forty-two patients were operated on, and showed gallstones either in the gallbladder or bile

TABLE 4—Findings in Operated Gallstone Cases Examined

Case	Sex*	Age	His- tory	Phys- ical Exami- nation	Roent- gen Ray	Duodenal Sediment			Pigments			Operative Findings
						Choles- terin	Bili- rubin	Bile- stained Cells	Uro bili- nogen	Uro bilin	Bili rubin	
1	♀	47	Pos	Pos	Neg	+	+	+	8	—	50	Gallstones
2	♀	44	Pos	Neg	Neg		+		0	—	24	Gallstones
3	♀	49	Pos	Ques	Neg		++		0	—	80	Gallstones
4	♀	40	Pos	Neg	Neg		++		0	—	90	Gallstones
5	♀	37	Ques	Neg	Ques	+	++		6	—	24	Gallstones
6	♀	47	Pos	Pos	Pos		++	+	0	—	21	Gallstones and diabetes
7	♂	45	Pos	Ques	Ques		++	+	5	—	100	Gallstones
8	♀	52	Pos	Ques	Neg		+		0	—	25	Gallstones
9	♀	25	Pos	Pos	Ques		++		5	—	30	Gallstones, no gallbladder
10	♀	35	Neg	Neg	Not done		++		0	—	250	Gallstones, ty- phoid carrier
11	♀	19	Misl	Misl	Neg		+	++	—	—	—	Gallstones
12	♀	39	Pos	Pos	Ques	++	++		0	—	80	Gallstones
13	♀	35	Pos	Pos	Ques	+		+	0	—	65	Gallstones
14	♀	42	Pos	Pos	Neg	+	++		0	—	200	Gallstones
15	♀	48	Misl	Ques	Neg	+++	+++		0	—	200	Gallstones
16	♀	12	Pos	Pos	Not done		++++		0	—	315	Gallstones, hemolytic jaundice
17	♀	64	Pos	Pos	Ques		+	+	0	—	117	Gallstones
18	♀	49	Ques	Ques	Not done		++++		48	—	98	Gallstones, diabetes
19	♀	50	Pos	Pos	Not done		+++		High			Gallstones, diabetes
20	♀	64	Pos	Pos	Neg	++	++		0	—	127	Gallstones
21	♀	17	Pos	Ques	Neg		+	+	Very high			Gallstones
22	♀	47	Pos	Neg	Ques		++	+	8	—	108	Gallstones
23	♀	73	Pos	Pos	Neg		++		Very low			Gallstones
24	♀	60	Neg	Ques	Not done	++	++		20	—	108	Gallstones in cystic duct
25	♀	42	Pos	Pos	Neg		++	+	0	—	28	Gallstones
26	♀	55	Pos	Neg	Ques	+	+++		6	—	172	Gallstones
27	♀	40	Misl	Neg	Neg	+	+	+	0	—	60	Gallstones
28	♀	53	Pos	Misl	Not done	++	+++		2	0	300	Gallstones
29	♀	56	Ques	Neg	Pos	+++	++		4	22	288	Gallstones, diabetes
30	♀	43	Pos	Pos	Neg	+	++		0	—	21	Gallstones
31	♀	45	Pos	Pos	Not done		+++		0	—	197	Gallstones
32	♂	24	Misl	Ques	Ques	+++			0	4	180	Gallstones
33	♀	33	Misl	Neg	Neg	+	+++		0	12	200	Gallstones, visceroptosis
34	♀	48	Ques	Pos	Neg		++	++	4	22	108	Gallstones
35	♀	40	Pos	Pos	Neg	++			22	40	108	Gallstones
36	♀	38	Pos	Pos	Neg		+	+	0	12	48	Gallstones
37	♀	52	Ques	Pos	Not done	++++	++++		5	12	120	Gallstones
38	♂	65	Pos	Pos	Ques		+++	+	0	4	50	Gallstones
39	♂	45	Misl	Ques	Neg		+	++	0	—	40	Gallstones
40	♂	42	Pos	Pos	Neg		++	+	4	—	22	Gallstones
41	♂	30	Pos	Pos	Ques		(rare)	++	30	20	100	Gallstones
42	♂	60	Neg	Ques	Ques		++	+	0	4	80	Gallstones, cirrhosis of liver

Pos, positive, Neg, negative, Ques, questionable, —, not done, Misl, misleading, +, present in abnormal amounts. As explained in the text, in many cases determinations for urobilin were not done.

\* In this column, ♂ indicates male, and ♀ female.

ducts. The remaining fifteen for various reasons did not undergo operation, but were discharged from the hospital with a flat diagnosis of cholelithiasis. They were seen by both medical and surgical consultants, who in every case agreed as to the diagnosis.

The results of the examination of the duodenal contents are given in Tables 3, 4 and 5. In Table 3 is given a summary of the findings in both groups of cases, together with the proportion of positive findings by history, physical examination and roentgen ray. Table 4 gives in detail the findings in the patients that came to operation, with a brief note as to any additional findings of interest. The results obtained in the unoperated patients are given in full in Table 5.

Before discussing the results obtained in this series of cases it is important to point out one essential difference between the findings here presented and those included in Table 2. In the previous group of pathologic controls, any sediment was considered abnormal that contained even rare amounts of either bile-stained cells or crystalline elements. In the present group of fifty-seven patients, no sediments

TABLE 5—Findings in Unoperated Gallstone Cases

Case	Sex	Age	His- tory	Phys- ical Exam- ination	Roent- gen Ray	Duodenal Sediment			Pigments			Discharge Diagnosis
						Choles- terin	Bil- rubin	Bile stained Cells	Uro- bil- nogen	Uro- bilin	Bil- rubin	
43	♂	49	Pos	+	Ques	+	++		0	—	38	Cholelithiasis
44	♂	54	Pos	Neg	Ques	++	+		8	—	430	Cholelithiasis
45	♂	70	Pos	Pos	Pos		++	+	8	—	216	Cholelithiasis
46	♂	59	Pos	Pos	Neg		+++		0	—	180	Cholelithiasis
47	♂	40	Pos	Pos	Neg	+	++		—	—		Cholelithiasis
48	♂	60	Pos	Pos	Neg		+++		0	—	40	Cholelithiasis
49	♂	16	Pos	Pos	Neg	++			0	—	150	Cholelithiasis
50	♂	53	Pos	Pos	Neg		+	+++	0	—	40	Cholelithiasis
51	♂	39	Pos	Pos	Ques	+	+		0	—	150	Cholelithiasis
52	♂	34	Pos	Pos	Neg	+	++		0	—	131	Cholelithiasis
53	♂	53	Pos	Pos	Not done		++		T	—	170	Cholelithiasis
54	♀	51	Pos	Ques	Ques		++	++	0	—	240	Cholelithiasis
55	♂	55	Pos	Pos	Not done		++	++	0	—	80	Cholelithiasis
56	♀	35	Pos	Ques	Ques		+		0	16	150	Cholelithiasis
57	♂	72	Pos	Pos	Ques	++	++	+	4	—	200	Cholelithiasis

The signs and symbols in this table are the same as those used in Table 4.

were considered of importance unless they contained easily recognizable amounts of one or the other element.

A brief description of the abnormal elements seen in the duodenal sediments under discussion is in order at this time. "Bile-stained cells" consisted either of leukocytes or of epithelial cells, the latter were round or columnar, and not infrequently whole layers of yellow columnar epithelium were observed, often in fan-shaped arrangement.

The abnormal crystalline elements, to which particular attention was paid, consisted in typical cholesterol plates, amorphous yellow bilirubin, and the darker yellow-brown granular crystals of calcium bilirubinate. As is to be seen in the tables, the individual crystalline elements were found alone or in combination with each other. As a rule the bile pigment crystals were composed of both types before mentioned, and are given together in Table 3. The accompanying illustration was prepared from a typical duodenal sediment obtained in a case of chole-

lithiasis, and shows all three crystalline elements. It was not at all uncommon to find conglomerate masses of cholesterol and pigment crystals, apparently very early stones in the making. In a typical case it was usual to find several large masses of abnormal crystals, as well as several smaller clumps in one cover-glass preparation.

Numerous other crystalline forms were also observed, but were not sufficiently characteristic to warrant classification. It is of interest, in view of the recent work of Rous, Drury, and McMaster<sup>22</sup> on the experimental formation of gallstones in animals, that frequently, in cases of gallbladder disease, masses of substances were observed which corresponded to the calcium carbonate crystals in the form of "spheruliths" or other shapes noted by these workers. Atypical cholesterol plates with pigment nuclei were also observed. The granular forms of calcium bilirubinate corresponded almost exactly to the "pigment nuclei" described by the foregoing authors. It is important, in this connection, to comment on the identification of the bile pigment crystals. Low power examination is usually sufficient to establish the identity of these crystals on account of the intensity of the yellow color. Degenerated biliary tract cells may, on casual examination, simulate the amorphous bilirubin crystals, but a careful glance under high power will readily distinguish between the two.

Examination of Table 3 indicates that in all but one of the fifty-seven patients abnormal crystalline sediments were found. Thirty-two of these sediments, or 56 per cent, showed large clumps of bile pigment crystals, twenty patients, or 35 per cent, showed a combination of cholesterol and pigment crystals, and four patients, or 7 per cent, showed only pure cholesterol. It is of interest to note that, in the patients undergoing operation, the three having pure cholesterol sediments showed practically pure cholesterol stones at exploration. In the majority of the remaining patients the stones were composed of cholesterol and bile pigment. In one patient with hemolytic jaundice (Case 16), pure pigment stones were found, corresponding exactly to the material obtained by duodenal drainage.

Of the fifty-seven patients, only one failed to show definitely abnormal amounts of crystals in the duodenal sediment. This patient (Case 41) did show rare clumps of bilirubin and a very large amount of bile-stained columnar epithelium.

Twenty-one of the patients with cholelithiasis, or 37 per cent, in addition to abnormal crystalline elements showed grossly abnormal amounts of bile-stained cellular material.

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<sup>22</sup> Rous, P., Drury, D. R., and McMaster, P. D. Observations on Some Causes of Gallstone Formation, *J. Exper. Med.* **26** 77, 1924.



## COMMENT

Analysis of the above figures shows clearly that in this unselected group of fifty-seven cases of cholelithiasis, practically all showed, on duodenal drainage, a sediment containing, in abnormal amounts, those crystalline elements chiefly concerned in the formation of gallstones. In addition, about one-third showed evidence of some biliary tract inflammation, as evidenced by the appearance of large numbers of bile-stained cells. Any attempt to localize the seat of stone formation, or of the irritative process by examination of the sediment, however, would be as fallacious as an attempt to localize genito-urinary pathology by examination of the urinary sediment.

A study of the foregoing results, and comparison of them with the data given in the group of other pathologic conditions (Table 2), would seem to indicate that in cases of cholelithiasis the duodenal sediment will reveal characteristic findings. In other pathologic conditions involving the biliary tract, the duodenal sediment may frequently show abnormal cellular or crystalline elements.

In any condition involving the biliary tract, it should be noted also that "casts" of bile-stained material are of frequent occurrence. They have been described by many observers, but are of little significance unless seen in abnormal numbers, as they are often found in normal duodenal sediments. A good description, together with illustrations of such "casts" or "bile thrombi," may be obtained in the article already alluded to, by Rous, Drury and McMaster.<sup>22</sup>

The main point of difference between the findings in cases of cholelithiasis and those in other diseases of the biliary tract, lies in the almost constant occurrence of large amounts of abnormal crystalline elements. I consider this point to be of real diagnostic significance.

The object of this investigation has been to ascertain, first, the constancy with which typical findings may be obtained by duodenal drainage in certain diseases, and second, to determine whether the results thus obtained warrant the use of the method as a diagnostic procedure. In another paper the writer has already shown the characteristic findings in infectious (catarrhal) jaundice. Similarly, examination of Tables 3, 4 and 5 indicates that in nearly all cases of cholelithiasis there is a typical set of findings, provided the proper technic is employed in the sedimentation of the duodenal contents. The additional finding of abnormal bile pigment values is suggestive but not diagnostic of biliary tract pathology. Other types of liver disease, as shown in data in Table 2, do not give constant results by duodenal drainage. The occurrence of such findings as those noted in Table 2, however, are strongly suggestive evidence of biliary pathologic changes, but are not diagnostic of any single disease entity.

The practical value of the method as a diagnostic procedure is indicated in Table 3. Of the fifty-seven patients with gallstones, five gave questionable histories, six gave absolutely misleading histories, and in three there was an entirely negative story. Thus, in nearly 25 per cent of the group, a carefully taken history was of little or no value. Similarly, in about 45 per cent of the patients, physical examination was of little or no value and in two cases was absolutely misleading. Roentgen-ray examination was not performed on every patient, but of the forty-seven patients so studied only twenty-two or about 45 per cent, suggested gallbladder pathologic changes. It is evident, therefore, that in an unselected group of cases of cholelithiasis, routine methods of examination are far from being infallible. Comparison of these data, with the findings made by duodenal analysis, would seem to indicate that a much higher percentage of positive results was obtained by the latter method than by the methods of diagnosis usually employed. It is far from being my intention to make fantastic claims for a method that has already been severely criticized because of immature and unwarranted assertions made in its behalf. It would seem however, that by strict adherence to a relatively simple technic, duodenal analysis promises much of value in diagnosis of diseases of the biliary tract, and particularly in the diagnosis of cholelithiasis. The very high proportion of positive findings in fifty-seven cases of cholelithiasis may have been fortuitous, and a similar analysis of a much larger series might show more negative results. It is my opinion, however, based on the foregoing data, and after examination of a large number of specimens of bile obtained at operation from the gallbladder or bile ducts, that abnormal crystalline elements are nearly always to be found in the presence of biliary calculi. I believe therefore, that duodenal analysis is of real diagnostic value, in spite of the time consumed, and the discomfort incident to the performance of the test. Like any laboratory test it is subject to error, and should not be employed in the place of ordinary and well-tried methods of examination. On the contrary, the only valid excuse for its existence is that it may be used as an additional diagnostic procedure.

The unfortunate manner in which the method has been employed by some physicians as a diagnostic and therapeutic measure for all ills, directly or indirectly related to the biliary tract, is greatly to be regretted. Unproved hypotheses have been welcomed by a few without due consideration for proper experimental evidence, and apparently have been used only as a basis on which to build a larger consultation and "special" practice. The psychologic effects produced by duodenal drainage have undoubtedly led, in some cases, to methods closely approximating charlatanry. It is to be hoped that the medical profession at large will assign to this procedure its proper place. It is, I believe, of undoubted

value, both as a therapeutic and diagnostic measure, but only in a selected group of cases, and only when performed in an intelligent and careful manner

#### SUMMARY AND CONCLUSIONS

1 The results of duodenal analysis in 274 cases is here reported. In addition to normal controls, 202 pathologic controls have been studied, including twenty-seven different disease entities. Fifty-seven cases of cholelithiasis have also been studied, in forty-two of which the diagnosis was proved by operative findings.

2 Analysis of the duodenal contents in these cases has consisted in spectroscopic estimations of the various bile pigments, and in the microscopic examination of the duodenal sediments for abnormal cellular and crystalline elements.

3 The importance of high-speed centrifugalization of the duodenal contents has been emphasized as the only means of securing consistent sediment findings.

4 Abnormal sediment findings have been found to consist of bile-stained epithelium or leukocytes, and cholesterol, bilirubin or calcium bilirubin crystals.

5 In cases of cholelithiasis, characteristic sediments have been found. These findings consist of abnormal amounts of any or all of the above named crystalline elements. Bile-stained cellular elements which are interpreted as suggestive of an irritative process in the biliary tract, are also found in a large proportion of these cases.

6 Other types of biliary tract disease, as a rule, also exhibit abnormal cellular or crystalline elements, but with no degree of constancy, and the findings in such cases are suggestive, rather than diagnostic. This statement is of particular interest in a differential diagnosis between chronic cholecystitis and cholelithiasis.

7 The results of bile pigment estimations in the cases studied tend to confirm previous investigative findings. As a rule, these estimations are definitely increased over normal in cases of increased blood destruction or in cases with functional disturbance of the liver.

8 The diagnosis and treatment of biliary tract disease by duodenal drainage, on the theory that magnesium sulphate instillations into the duodenum produce gallbladder contractions and subsequent drainage, is criticized, on the basis of clinical and experimental observations. Deductions as to the localization of biliary tract pathologic changes on the basis of so-called "A," "B" and "C" biles are similarly criticized.

9 A conservative use of duodenal analysis as a therapeutic and diagnostic measure in carefully selected cases is advocated.

# TREATMENT OF ASTHMA WITH AUTOGENOUS VACCINES \*

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It has been recognized that the greatest stumbling block in the treatment of asthma is infection and, until some method is developed which may be a guide to vaccine therapy its results will be uncertain. No authoritative work has appeared in the literature to solve this difficult problem. In fact, marked difference of opinion still exists regarding the rôle played by bacteria in the causation of asthma and the value of vaccines in its treatment.

No theory is here offered as to the cause or the relief of asthma, but we do wish to present a clinical method of study and treatment which has appeared to produce in a small series of cases a large percentage of favorable results. We have attempted to free our minds of preconceived ideas and prejudices and to examine the question from the clinical point of view, submitting the method to the verdict of result obtained.

Sixty-two cases of asthma and asthmatic bronchitis, tested and treated with autogenous vaccines in the asthma clinic of St. Luke's Hospital and in private practice, form the basis of this report. The method of testing with autogenous vaccines has been described elsewhere<sup>1</sup>. Before considering the advisability of treatment with vaccines we subjected all of our patients to a physical examination and to cutaneous tests for hypersensitiveness to foreign proteins. Where such hypersensitiveness was demonstrated in apparent causal relation to the asthmatic condition, an effort was made to separate the patient from the offending protein or, when indicated, to desensitize him. In many instances surgical treatment was obtained for gross obstructions in the nasal passages and nasopharynx, and for infected nasal sinuses, tonsils and teeth. In addition, some form of medication was prescribed, and some of these patients were put to bed at home or in the hospital.

During this preliminary period of observation and of symptomatic or specific treatment, which was rarely shorter than two weeks, a considerable number of patients were relieved of their asthma, and consequently did not receive vaccine treatment and are not included in this

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\* From the wards and asthma clinic of St. Luke's Hospital.

<sup>1</sup> Thomas, W. S., Famulener, L. W., and Touart, M. DeM. This issue, page 85.

series The remaining sixty-two cases were tested with autogenous vaccines and received therapeutic inoculations in accordance with the results of those tests In all cases, ample opportunity was provided for remedial measures other than autogenous vaccines to produce a therapeutic effect before the latter were used

In the preparation of test vaccines, cultures were made from various sources depending on the indications in each particular case Where sputum was obtainable it was always used, as was also aspirated material from infected accessory nasal sinuses Cultures were sometimes made from excised tonsils and directly from the nares, pharynx and the tonsils in situ In certain instances, either because of some clinical indication or because of failure to obtain positive reactions with bacteria from other sources, cultures were made from the stool

All organisms recovered from every source were made into vaccines, and with these vaccines intracutaneous tests were made and the readings interpreted as described in the paper before mentioned <sup>1</sup>

It not infrequently happened that definite clinical improvement was noted within a few hours after the tests were made In seven cases this amounted to complete and in three to complete and permanent relief Vaccine treatment was begun as soon as possible after decisive information had been obtained from the tests, usually from three to five days Occasionally only one organism was chosen but it more often happened that two or more gave sufficiently active reactions to be included The treatment vaccines were separate suspensions of each organism in physiologic sodium chlorid solution in water, plus 0.25 per cent tricresol, each cubic centimeter containing approximately one billion organisms At times, combined vaccines of two or more organisms were used With some of the more toxic bacteria, notably *Streptococcus hemolyticus* and the Friedlander bacillus, the treatment dilution was reduced to five hundred million organisms in each cubic centimeter The advantage in administering each type of organism separately is that it is then possible to judge accurately its effects by the size and severity of the local reaction

In this method of vaccine therapy our purpose has been to produce in healthy tissue, at frequent intervals, a local reaction characterized by slight swelling and tenderness, and perhaps erythema of the overlying skin, lasting from one to five days The initial dose was approximately one hundred million organisms of each treatment dilution, and if this dose produced such a local reaction it was repeated at intervals of two or three days until none followed In the event of failure to produce a local reaction or when a previously sufficient dose ceased to cause such a reaction, the amount was increased by one hundred million organisms on each occasion until the desired result followed It seldom happened that the dosage exceeded four hundred million organisms at any time

during the treatment. As the asthma improved, the interval between doses was increased first to five and later to seven days. Rapid and uninterrupted recovery occurred in a few patients, but the usual course was gradual improvement, varied from time to time by exacerbations of the asthma. In most of these patients vaccines were discontinued as soon as relief of symptoms and physical signs occurred. Finding, however, an occasional tendency to relapse after an interval of weeks or months, the more recent patients have been treated with weekly, bi-weekly or monthly doses long after the occurrence of clinical relief. In so doing we are in accord with a recently published statement of Rackemann,<sup>2</sup> to the effect that the prolonged use of vaccines appeared to prevent relapses. The duration of treatment varied from one to ten weeks and averaged about six weeks, the number of vaccine doses varied from one to thirty and averaged about fifteen. Where symptoms continued unabated after six or ten inoculations, fresh cultures were made, at times disclosing the presence of organisms hitherto undiscovered.

The important factors in the use of vaccines in our experience seem to be (1) proper selections by the intracutaneous test, (2) preparation of each organism in a separate vaccine, (3) the use of a therapeutic dose just sufficient to produce a mild local reaction, (4) adherence to this dose so long as it continues to produce such a reaction, then increasing it, (5) frequent dosage early in the treatment with a gradually lengthened interval, followed by (6) prolonged administration at relatively long intervals.

#### REPORT OF CASES

CASE 1—F. M., a man, aged 75, was admitted to the hospital, Jan. 23, 1923, complaining of cough with expectoration, and paroxysmal dyspnea of twenty years' duration, which had recently become so severe as to incapacitate him.

*Physical Examination*—Emphysema, chronic bronchitis with asthma and myocardial insufficiency were the chief findings. Dermal tests for hypersensitivity to food and air borne proteins were followed by negative reactions. Intracutaneous tests with autogenous vaccines made from sputum produced a sharp late reaction to *Staphylococcus aureus* and *Micrococcus catarrhalis*. Treatment was instituted with vaccines of these organisms administered every second day. The patient was discharged from the hospital February 20, completely relieved. On September 25, a letter was received stating that complete relief continued.

CASE 2—J. B., a man, aged 77, was admitted to the hospital Jan. 16, 1923, complaining of cough and paroxysmal dyspnea for the last year, at first nocturnal but lately continuous. There had been no previous attack.

*Physical Examination*—The findings were those of chronic bronchitis, with asthma and emphysema and myocardial insufficiency. The patient's mother was asthmatic and his father died of tuberculosis. Cutaneous tests with food and air borne protein were followed by negative reactions. Intracutaneous tests with vaccines of all the organisms isolated from the sputum produced both early and late positive reactions to *Staphylococcus aureus* and *Bacillus coli communis*. Vaccines from these, in proper dilution, were consequently administered at intervals of two days until April 2, when he was discharged completely relieved.

<sup>2</sup> Rackemann, F. M. J. Immunology, August, 1923.

He returned to the hospital November 18, stating that he had suffered from a relapse for the last three weeks. A new bacterial flora was isolated from his sputum, and when tested sharp late positive reactions to *Streptococcus viridans*, strain 3, and *Micrococcus catarrhalis* were obtained. He likewise reacted sharply to a stock *Bacillus coli communis* vaccine. He was accordingly treated with the vaccines of these organisms with prompt relief of symptoms. He was discharged completely relieved December 12.

CASE 3—M S, a man, aged 38, had slight asthma from infancy, but for five months previous to November, 1922, had suffered severely and continuously and had lost 40 pounds (18 kg) in weight and correspondingly in strength. He had received active treatment of various sorts, including autogenous vaccine therapy, in hospital, and was treated otherwise in several health resorts without avail.

He was found to be sensitive to all available feather proteins and was carefully removed from contact with them without obtaining relief.

His sputum on culture yielded pneumococcus type 3, *Staphylococcus albus* and *Streptococcus viridans*. He reacted actively both early and late to the pneumococcus and received therapeutic inoculations with the same. Prompt improvement occurred and on again removing him from contact with feathers, the patient experienced complete relief after two months of treatment. He was then able to sleep on a feather pillow again, and to live at home where he kept chickens and canaries.

A slight relapse occurred in October, 1923, at which time his left antrum was found to contain pus and was washed out. The material yielded *Micrococcus catarrhalis*, staphylococcus and pneumococcus, Group 4. The pneumococcus could not be grown sufficiently to make a vaccine, but vaccines of the other organisms were prepared and he was tested with them but no reactions were obtained. The patient then received inoculations with the former vaccine, he experienced relief at once and remains entirely free of asthma to date.

#### COMMENT

In classifying our results we have used the following terms: (1) relieved, denoting complete and at last report permanent relief, (2) markedly improved, denoting that subjectively and objectively the patient was relieved of most of his symptoms even though some asthma continued in the form of isolated paroxysms or as dyspnea on exertion or when exposed to irritating vapors, dust or wind, (3) recent, denoting that these cases are still under treatment and, though relieved or markedly improved, the final result is still undetermined, (4) failure, denoting those cases where relief was slight or temporary or where no improvement occurred.

The result of the whole series is shown in Table 1. Of sixty-two patients treated, thirty-two, or 51.6 per cent, are completely relieved of

TABLE 1—*Asthma and Asthmatic Bronchitis Tested and Treated with Autogenous Vaccines*

	Number		Per Cent
Relieved	32	or	51.6
Much improved	14	or	22.6
Recent, relieved under treatment	8	or	12.9
Failures	8	or	12.9
Total	62	or	100.00

their asthma, fourteen, or 22.6 per cent, are markedly improved, eight, or 12.9 per cent, are recent, and eight, or 12.9 per cent, were failures.

Advanced age did not appear to be an important factor in the prognosis. In Table 2 the sixty-two cases are arranged in age groups. Our

TABLE 2—*Ages and Results, Sixty-Two Cases of Asthma and Asthmatic Bronchitis Tested and Treated with Autogenous Vaccines*

Results	Age Groups			
	1 to 20 Years 7 Cases	21 to 40 Years 19 Cases	41 to 60 Years 27 Cases	61 to 80 Years 9 Cases
	Pr Ct	Pr Ct	Pr Ct	Pr Ct
Relieved	57	36	55	66
Much improved	0	26	22	33
Recent, relieved under treatment	28	16	11	0
Failures	14	21	11	0

youngest patient was aged 7 years and completely relieved, and our oldest was 77 years and completely relieved. Sixty per cent of these sixty-two patients were over 40 years of age, and there were nineteen between 50 and 60 years.

In Table 3, the thirty-two completely relieved patients are grouped according to the duration of their asthma. Long duration of the asthma

TABLE 3—*Duration of Asthma in Thirty-Two Cases Completely Relieved After Treatment with Autogenous Vaccines*

Duration	Number of Cases
1 year or less	1
1 to 5 years	19
6 to 10 years	6
10 years or longer	6

did not seem to influence the result unfavorably. For example, two of these patients were asthmatic from infancy. They were aged 38 and 50 years respectively.

Table 4 shows the duration of relief in the same thirty-two cases. As indicated in the footnote, six of them have had relapses but were

TABLE 4—*Duration of Complete Relief in Thirty-Two Cases of Asthma Treated with Autogenous Vaccines\**

Duration	Per Cent
1 month	3.00
2 to 6 months	37.5
7 to 12 months	40.7
13 to 18 months	9.4
Not followed	9.4

\* Six patients relapsed but were promptly relieved after further vaccine treatment.



promptly relieved after further vaccine treatment. Nineteen were examined during the month in which this was written, three during the previous month, six at various intervals back to five months before, one died from apoplexy after five months of entire relief and three were not traced.

Eight failures are reported. Of these, four are now under observation for further study, and individually present the following conditions which may have contributed to the failures.

Case 1—Unresolved interlobar pleurisy and radiographic evidence of pulmonary tuberculosis.

Case 2—Purulent bronchitis, yielding organisms in the sputum not previously recovered in our cultures and consequently not used in tests and treatment.

Case 3—Purulent pansinusitis with nasal polyp and a new bacterial flora in the sputum.

Case 4—Clinical and radiographic evidence of pulmonary tuberculosis.

Of the remaining four, whom we have not been able to follow, one had, when last seen, purulent ethmoiditis with nasal polyp, unrelieved by surgical treatment and vaccines.

#### SUMMARY

1 The reactions to intracutaneous tests with autogenous vaccines were studied in sixty-two patients with asthma and asthmatic bronchitis.

2 These sixty-two cases received therapeutic inoculations with autogenous vaccines selected in accordance with the results of these tests.

3 In 12.9 per cent no improvement was obtained, but complete relief or material improvement followed in 87.1 per cent.

# AUTOGENOUS VACCINES IN DIAGNOSIS, WITH SPECIAL REFERENCE TO ASTHMA \*

## PRELIMINARY REPORT

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AND

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Specific reactions by the human skin to certain organic substances are important aids in diagnosis. Skin tests with air borne and food proteins, as guides in determining the exciting causes of asthma and allied disorders, have found a place in company with the Schick, the luetin and the dermal tuberculin tests. Less attention has been directed toward tests with bacterial vaccines in the infected and hypersensitive patient, indeed, their importance has been questioned. A few investigations in vaccine skin testing have been published by others, who report suggestive but confusing results. The difficulties encountered in making an adequate study of this problem from the bacteriologic standpoint have, perhaps, accounted for some of the earlier failures.

On beginning the study of a case of asthma or allied disorder, air borne and food proteins as etiologic factors should be eliminated, if possible, by proper skin tests. Positive skin reactions to one or more of these proteins are encountered in a little over one-half of all patients thoroughly tested. In the event of a complete series of protein tests with negative reactions, or in case of failure to relieve symptoms by treatment, as indicated by the reactions, a bacteriologic survey of the case should be undertaken. Asthmatic patients have been encountered who were hypersensitive to food or air borne proteins, but who were not completely relieved of their symptoms when separated from their offending proteins. Several of them were found to give positive skin reactions to autogenous vaccines, and were entirely relieved by vaccine treatment as indicated by the reactions to vaccine tests. These patients were apparently hypersensitive to bacterial proteins as well as to those of foods or those air borne.

The basic requirement is a thorough and most exacting bacteriologic examination of materials from all possible foci of infection. Attention is chiefly directed to a study of materials from the nasal cavity and accessory sinuses (in particular, the ethmoids and antrums), infected adenoids, tonsillar material from the crypts, pus, if present, sputum from the deeper air passages (Table 1), also the feces.

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\* Read before the New York County Medical Society, Dec 19, 1923

Besides the four principal foci (nasal cavity with accessory sinuses, tonsils, lungs, intestinal tract), other possible sites should be considered, such as apical abscesses of the teeth, gallbladder infection (duodenal contents), infected endometrium, seminal vesicles, prostate and urinary tract. The clinician, in the physical examination of his patient, should search for all possible foci of infection. Material from infected foci should be collected and submitted to the bacteriologist for the isolation and identification of organisms present.

The methods employed in the collection of material for bacteriologic examination have a considerable bearing on final results. Great care should be exercised to exclude extraneous contaminants and an aseptic technic is essential in all cases. Nasal discharges may be collected with

TABLE 1—*Incidence of Bacteria Found in the Sputum of 180 Patients Examined*

	Times
<i>Streptococcus viridans</i>	311
<i>Chromogenic coccus</i>	62
<i>Staphylococcus aureus</i>	51
<i>Staphylococcus albus</i>	50
<i>Streptococcus hemolyticus</i>	42
<i>Atypical gram-negative coccus</i>	34
<i>Atypical gram-negative bacillus</i>	30
<i>Pneumococcus</i>	25
<i>Micrococcus catarrhalis</i>	13
<i>Streptococcus indefinite</i>	12
<i>Enterococcus</i>	11
<i>Bacillus coli communis</i>	9
<i>Bacillus fecalis alkaligenes</i>	9
<i>Micrococcus albus</i>	8
<i>Staphylococcus aureus hemolyticus</i>	7
<i>Bacillus Friedlander</i>	4
<i>Staphylococcus albus hemolyticus</i>	3
<i>Staphylococcus citreus</i>	3

sterile cotton swabs, or, if copious, in sterile gauze wipes. Tonsillar exudate or pus may likewise be collected on sterile cotton swabs, care being taken to prevent contamination with saliva. If it is impracticable to make cultures at once, the swabs containing the material should be replaced in the sterile test tube, plugged with a sterile cotton stopper and sent to the laboratory to be immediately cultured. Sputum or feces should be collected directly in sterile jars and placed on ice, if it is impossible to culture at once. In private practice, material collected on sterile cotton swabs may be seeded at once on the surface of solid culture mediums (blood agar slants and Loeffler's serum medium) and sent immediately (with collecting swab in sterile plugged test tube) to the bacteriologic laboratory for examination.

It is essential in the bacteriologic examination of specimens that a careful study of stained films of the original material is made, as a

guide to the bacterial flora present, and that it be cultured on special or enriching mediums, as indicated. Further, the study of stained films of the original material offers a means of determining whether or not all types of organisms present develop later in the cultures. If not, further attempts should be made to culture and isolate all organisms that were found in the original material. Types of organisms not found at first are occasionally obtained by subsequent cultures of new material from the same source. The recurrence of symptoms in a treated case, after a quiescent period, calls for a repetition of the full bacteriologic examination in order to determine if infection with other types of organisms has supervened.

As a routine laboratory procedure, the materials are cultured directly on human blood agar slant and in dextrose nutrient broth, also a portion is emulsified in broth from which seedings are made by the dilution method in a series of poured blood agar plates. After the proper period of incubation has elapsed, stained preparations are made of the organisms which have developed from the original cultures in the blood agar slants and in the dextrose nutrient broth inoculations. The organisms present are carefully studied microscopically to identify the types, and steps are taken then for the isolation and cultivation of each species or strain. The primary blood plates are examined especially for hemolyzing types of organisms, and fishings from colonies are transferred to suitable culture mediums.

After cultivation, isolation and identification of the bacterial strains present in a given specimen, it is necessary to prepare vaccines both for testing and for therapeutic purposes. Without going into full details of the technic of culturing and killing organisms usually employed in the preparation of a bacterial vaccine, it is sufficient to state that the organism is ordinarily cultured either on plain nutrient agar slants or in dextrose nutrient broth, dependent on the particular species. Ultimately they are killed by heating for one hour at 60 C, or at 65 degrees, if necessary.

The standardization of the vaccine is based on the method published by Hopkins<sup>1</sup>. The Hopkins method offers a means by which an accurate measurement by volume of the thoroughly packed moist organisms may be made in a special type of centrifuge tube. A 1 per cent suspension in physiologic sodium chlorid solution is prepared from the measured packed bacterial residue, then the organisms are killed by heat. Controls for sterility are made, after which sufficient tricresol solution is added to give an 0.25 per cent concentration. Instead of standardizing the original 1 per cent suspension by determining the number of organisms

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1 Hopkins, J. G. A Method for Standardizing Bacterial Vaccines, J. A. M. A. 60 1615 (May 24) 1913

present in 1 c c , as advised by Hopkins, a unit valuation has been placed on the volume content of bacterial substance present in such a suspension. The unit consists of that amount of bacterial substance which is present in 0.01 c c of a 1 per cent suspension of the organism prepared under certain fixed conditions.<sup>2</sup> Experience has shown that this quantity (one unit) of vaccine is, perhaps, the most favorable amount to produce a skin reaction when applied intradermally in the hypersensitive patient. The 1 per cent suspension of killed organisms, prepared by the Hopkins method, is designated "vaccine stock," and is supplied in small ampules for the intradermal tests. The vaccines for therapeutic purposes are prepared from the "vaccine stock" which contains 100 units per cubic centimeter. Dilutions in physiologic sodium chlorid solution containing 0.25 per cent tricesol are made to include the number of units per cubic centimeter desired by the clinician.

In establishing a vaccine unit, based on a known amount of bacterial substance present in a suspension, an attempt has been made to obtain (1) uniformity in dosage, (2) comparable valuations of vaccines prepared from different species of organisms and (3) constant valuation for vaccines made from the same bacterial species. Experience has shown that by the commonly employed methods of counting, inaccuracy in results may occur. Emphasis must be placed on the exacting technical character of the laboratory work, which demands the best efforts of a highly trained bacteriologist. The clinician's success in diagnosis and treatment of the class of patients under consideration here is dependent on the full cooperation of the laboratory specialist.

Each test injection is made with a freshly sterilized tuberculin syringe and a needle of fine caliber, with which the control solution and each vaccine are introduced intradermally, so that minute wheals are seen. The amount of test vaccine used in each instance is regularly 0.01 c c. The scratch or dermal tests made with so-called proteins prepared from bacteria have been tried and have been found to be unsatisfactory.

As a control, in each series of tests, the same diluent of sodium chlorid and tricesol solution is used as that employed in diluting the vaccines. The injections are made in a row, usually on the arm or forearm, which traverses the limb in a spiral direction, the distance between the points being at least  $1\frac{1}{2}$  inches (3.30 cm). The oblique line is preferred because of the occurrence, in about 4 per cent of the cases, of a reaction severe enough to cause a transitory lymphangitis producing a pink flush extending for several inches up the limb. Should this erythematous area cross another point of injection the result would be confusing.

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2 This phenomenon occurred in 4 per cent of the positive late reactions.

The positive reactions following these tests are of two separate types (1) an early reaction, appearing in from ten to thirty minutes and soon thereafter fading, (2) a late positive reaction, noticeable in twelve hours or less, and at its height on the second day. It persists for from two to five days, and, under certain circumstances, for several weeks.

1 The early positive reaction is a wheal at least 1 cm in diameter, with pseudopodia or grossly irregular outline, sharply marked off from a surrounding pink areola. Early positive reactions have been observed in thirty-five of 134 asthmatic and hay-fever patients (about 25 per cent), but are rarely seen in other than this type of patient (Table 2). The majority of these 134 patients were nonsensitive to skin tests with air borne and food proteins.

TABLE 2—*Organisms from All Sources Causing Early Positive Skin Reactions (Wheals with Pseudopodia) in 44 Out of 180 Patients Tested*

	Times
Staphylococcus aureus	12
Streptococcus viridans	11
Chromogenic coccus	8
Staphylococcus albus	6
Pneumococcus	5
Atypical gram-negative bacillus	4
Bacillus coli communis	4
Streptococcus hemolyticus	4
Micrococcus catarrhalis	3
Bacillus Friedlander	1
Bacillus fecalis alkaligenes	1
Bacillus typhosus	1
Enterococcus	1
Staphylococcus citreus	1

2 The late positive reaction is not unlike the Schick reaction in appearance, but in order to read and interpret its significance, the component features must be noted by touch as well as by sight, and recorded graphically, as they change from day to day. The chart enables one to decide which, if any, of the organisms used in testing should be employed in treating the patient.

#### COMMENT

Any of the following features may appear about the point of injection during the first twenty-four hours and may persist for five or more days following the test: (1) an indurated, slightly elevated nodule, usually about 0.5 cm in diameter, (2) redness of the skin over the nodule, (3) a surrounding pink flush or zone of erythema, from 1 to 10 cm in diameter, the so-called areola, (4) tenderness on pressure, usually occurring at the nodule only, but sometimes extending over the

whole areola, (5) heat, felt by the palpating finger, (6) lymphangitis,<sup>3</sup> lasting from one to three days, not necessarily associated with a pustule, but commonly with enlarged, tender glands, (7) slight fever and malaise occasionally accompany marked late positive reactions, (8) pustule<sup>3</sup>

Late reactions to the different types of organisms vary somewhat Staphylococci and streptococci regularly, but the intestinal group of bacilli less often induce the indurated nodule Positive reactions to

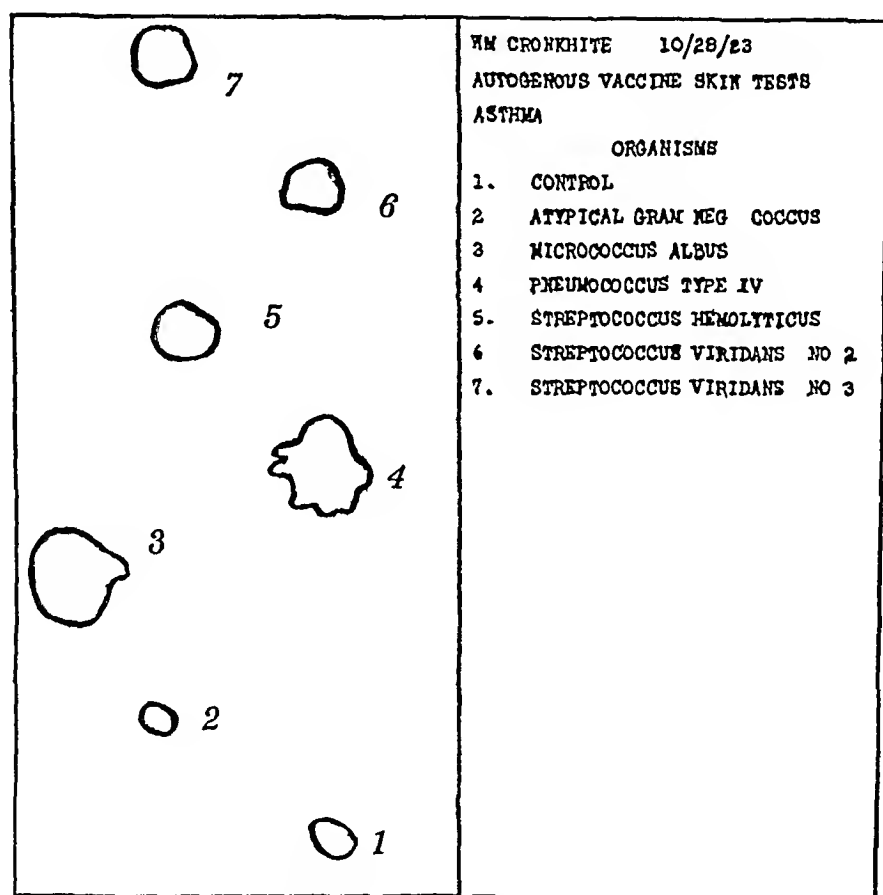


Fig 1—Early (half hour) reactions, as recorded in the text

bacilli of the colon-typhoid group give large, hot areolae which fade in two or three days or more The nodules caused by streptococci frequently persist for many days, or even weeks, sometimes becoming pigmented and occasionally showing desquamation

Positive reactions, whether early or late, are considered to be of equal importance as indications for the therapeutic use of the vaccines which produced them

3 A small sterile pustule at the point of injection was observed in about 4 per cent of those patients who gave late positive reactions Rarely has it been associated with a small slough

In reading and recording the early reactions, the circumference of the wheal is outlined on the skin with pen and ink, and numbered. When dry, this picture is transferred to wet blotting paper laid on it (Fig 1) and later filed for record.

Those features comprising the late reactions are recorded in charts as shown in Figure 2, A and B, in which N denotes an indurated nodule 0.5 cm in diameter, two N's *vertically placed*, a nodule twice as large, R denotes redness at point of injection, RR, a deeper red color, T denotes tenderness on pressure, TT, exaggerated tenderness, A denotes a surrounding areola 1 cm in diameter, AA, an areola 2 cm in diameter, etc.

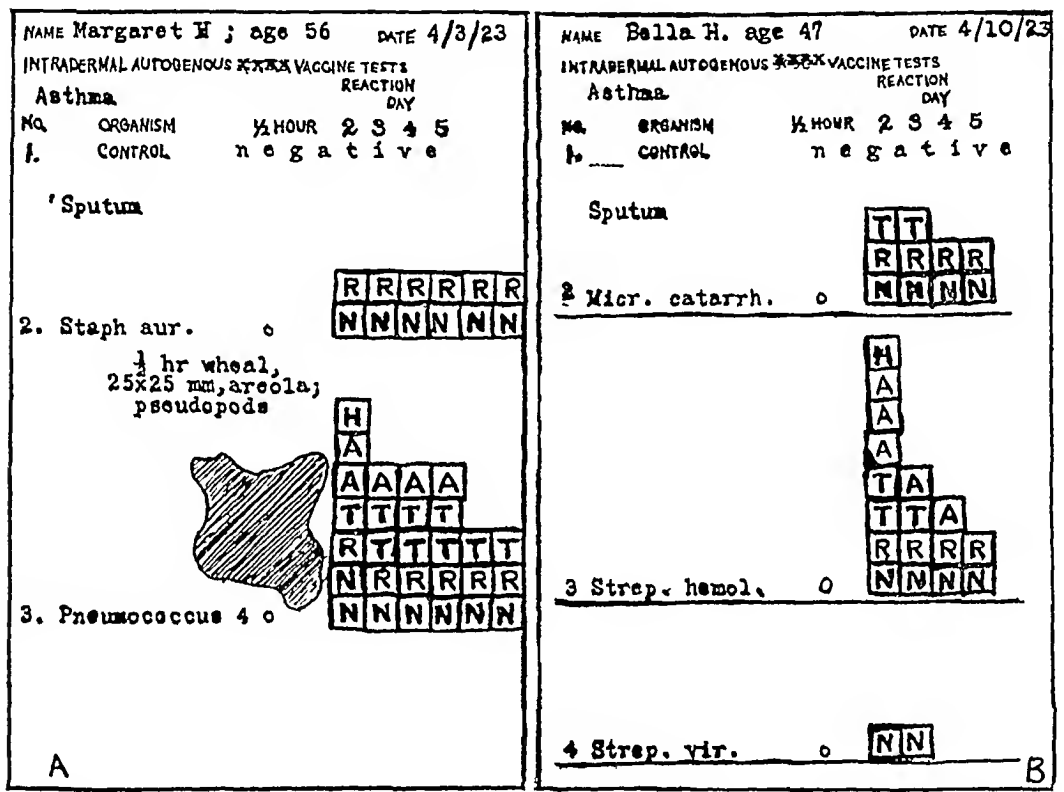


Fig 2—A, early positive reaction to pneumococcus, type 4, moderate late reaction to *Staphylococcus aureus*, and marked late positive reaction to pneumococcus. B, late positive reaction to *Streptococcus hemolyticus*, negative late reactions to *Micrococcus catarrhalis* and *Streptococcus viridans*. All early (half hour) reactions are negative.

(such areolae sometimes reach a diameter of 10 cm), H denotes heat of nodule or areola as felt by the palpating finger, P denotes pustule, G denotes enlarged glands and includes lymphangitis.

Observations of the findings must be recorded daily over a period of at least five days, if persisting (Fig 2).

SUMMARY

A late reaction is considered to be positive when, in addition to the features of the control injection, it exhibits during a period of five



days or longer, two or more of the before mentioned component parts. A positive reaction is not what appears at any one time, but is the aggregate of what is seen and felt at the site of the test during the five or more days following it. Such a chart as is shown in Figure 2 affords an efficient and almost indispensable means of depicting all of each reaction's features as they come and go.

A negative skin reaction to an autogenous vaccine is taken to indicate that the organism is innocuous to its host. However, vaccines made of organisms commonly considered to be nonpathogenic have often produced positive skin reactions, and when used in treatment have given relief of symptoms. It is evident, therefore, that test vaccines should be prepared from all types of organisms recovered from the patient.

Oversedoses of vaccines, either in testing or treatment, have been followed by asthmatic seizures in ten of our patients, and in one of them on three occasions. A phenomenon not infrequently observed following the injection of a treatment vaccine is the lighting up of faded test reactions to the same bacterium.<sup>4</sup>

Studies in this field during the last three years have yielded sufficient data to encourage the belief that by means of preliminary skin testing, properly conducted, vaccine therapy may be put on a firmer footing. It is believed that by this method it may be possible to decide which of several autogenous vaccines should be used in treatment, or whether any vaccines should be used. False hope of cure by autogenous vaccine treatment in cases which show no positive reactions is averted. That these positive skin reactions to vaccines are not chance phenomena has been indicated by the positive results of repeated tests on the same person, and especially by the favorable results of vaccine treatment conducted in accordance with them. Of sixty-two patients suffering with asthma so treated, fifty-three have been either completely relieved or materially improved.

NOTE—Autogenous vaccine skin tests and treatment have been conducted by the authors during the last two years on patients suffering with perennial hay-fever, intestinal infections, arthritis, eye infections, dermatoses and pneumonia. It is planned to publish the work and its results in the near future.

St. Luke's Hospital

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<sup>4</sup> Such a recurring reaction in one patient eventually formed a sterile pustule.

# A CASE OF PELLAGRA—ITS BEARING ON THE ETIOLOGY AND CURE OF THE DISEASE

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It seems to have been fairly well established that poor or insufficient food, *per se*, does not cause pellagra. The epidemiologic observations of Goldberger<sup>1</sup> in 1914 furnish rather conclusive evidence that the disease is not bacterial in origin or transmissible by insect bites. To quote from Goldberger: "The investigations of the Public Health Service now permit one to answer the oft-repeated question 'Is pellagra catching?' in the negative. No germ that can properly be considered the cause of the disease has ever been found. Attempts to give persons pellagra by inoculations of the blood, saliva, or other body discharges from several cases of pellagra have failed completely. Furthermore, in an asylum where many of the inmates developed pellagra year after year, it was observed that the nurses and helpers who lived with them never developed the disease."

The work of White<sup>2</sup> and of Stannus<sup>3</sup> in which both observers were able to eradicate pellagra, in the first instance from a camp of Armenian refugees, and in the latter instance from the Central Prison of Nyasaland, by changing the diet only, all other conditions remaining the same, also points against its bacterial origin. It seems reasonably certain, therefore, that in pellagra we are not dealing with a disease caused by bacteria. Just what dietary factors are involved in the causation of pellagra has not been fully determined. As far back as 1866, Roussel (cited by Goldberger) ascribed to milk a very important place in its prevention. Lombroso<sup>4</sup> taught that a diet rich in meat was valuable in the prevention and cure of pellagra.

An epidemiologic study of the disease by Goldberger, Waring and Willets in an orphanage at Jackson, Miss., in 1915, disclosed the fact that only inmates between the ages of 6 and 12 years were affected. It was further observed that the diet of the affected group contained a disproportionately small amount of lean meat or other animal proteins. These investigators suggested at that time that prevention of the disease might be worked out if the diet were corrected to include more fresh meat, eggs, and milk. In order to test out further this conclusion, Gold-

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1 Goldberger. Public Health Report Reprint, No 461, 1914, pp 6-7

2 White. Report of an Outbreak of Pellagra Amongst Armenian Refugees at Port Said, 1916-1917

3 Stannus. Tr Roy Soc Trop M & Hyg, 1920, p 16

4 Lombroso. Die Lehre vonder Pellagra, Berlin, 1898

berger and Wheeler,<sup>5</sup> in 1915, at the Mississippi State Penitentiary undertook to produce pellagra experimentally in eleven volunteer inmates of the prison by the exclusion of fresh meat, milk, and eggs. As a result of this experiment, six out of the eleven men showed symptoms distinctive of pellagra, while in thirty-five controls living under the same conditions, but allowed meat and milk, no case of pellagra was observed. The diet on which the eleven men were fed was not deficient in antineuritic, antiscorbutic, or fat soluble A vitamin, nor was it deficient in the quantity of food consumed. To quote the conclusions of these observers: "So that of the now generally recognized essential dietary factors there remain for consideration as possibly essential in relation to the etiology of pellagra, the protein (amino-acid) and the inorganic factor."

The studies of Osborne and Mendel,<sup>6</sup> McCollum<sup>7</sup> and his associates, and more recently Wilson,<sup>8</sup> confirm this view. That the protein element in the diet is an important factor is shown by the work of Goldberger, Waring and Willets<sup>9</sup> in their attempt to prevent the disease in the Georgia State Sanatorium and in two orphanages. Following modifications in diet to include more proteins, not one of seventy-two pellagrous persons in the Georgia institution developed evidence of a return of the disease. In one of the orphanages, in 172 pellagrous children there was only one recurrence, and in the other orphanage not a single case appeared in 168 nonpellagrous inmates. These observations were made over a year's interval of time. In studies derived from clinical experience, it is important that evidence bearing on this protein deficiency conception of the disease should be published.

The following case which I report should be placed on record, first, because it supports the defective protein theory relative to the etiology of the disease, in that the patient had been deprived of meat for about two years prior to the onset of the attack, second, because of the prompt recovery on a generous meat diet and the use of sodium cacodylate intravenously, and, third, because it is the first case to be reported from South Dakota, a supposedly nonpellagrous area.

#### REPORT OF CASE

Mrs. E. B., aged 50, married, the mother of three children, living at Mellette, S. D., was referred by Drs. Kleger and McCauley, March 29, 1923, complaining of nervousness, soreness of the mouth, diarrhea, and a dirty brown rash over

5 Goldberger, Joseph, and Wheeler, G. A. Experimental Pellagra in White Male Convicts, *Arch. Int. Med.* **25**: 451 (May) 1920.

6 Mendel, L. B. Nutrition and Growth, *J. A. M. A.* **64**: 1539 (May 8) 1915.

7 McCollum, E. V. *J. A. M. A.* **71**: 937 (Sept. 21) 1918.

8 Wilson. *Hygiene* **20**: 1-59, 1920.

9 Goldberger, J., Waring and Willets. *U. S. Public Health Reports* **30**: 3117-3131, 1915.

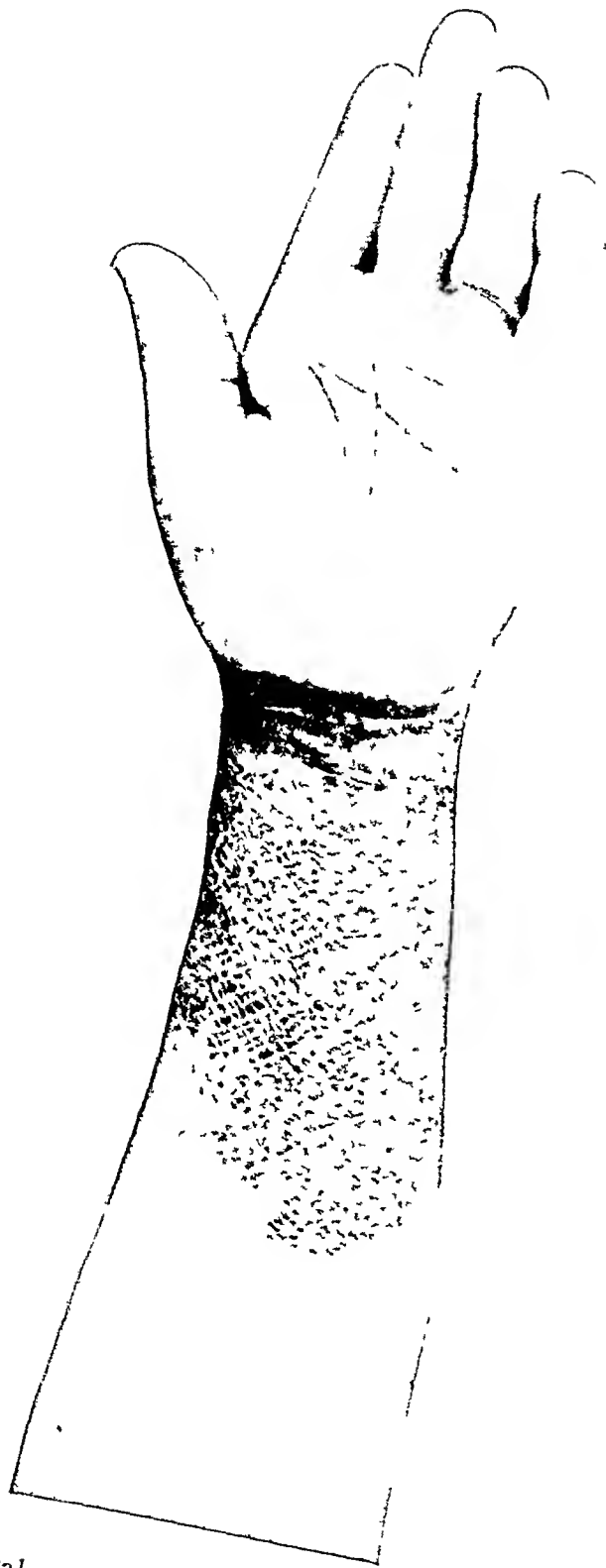


Fig 1—Ventral view of the left hand of Mrs K B

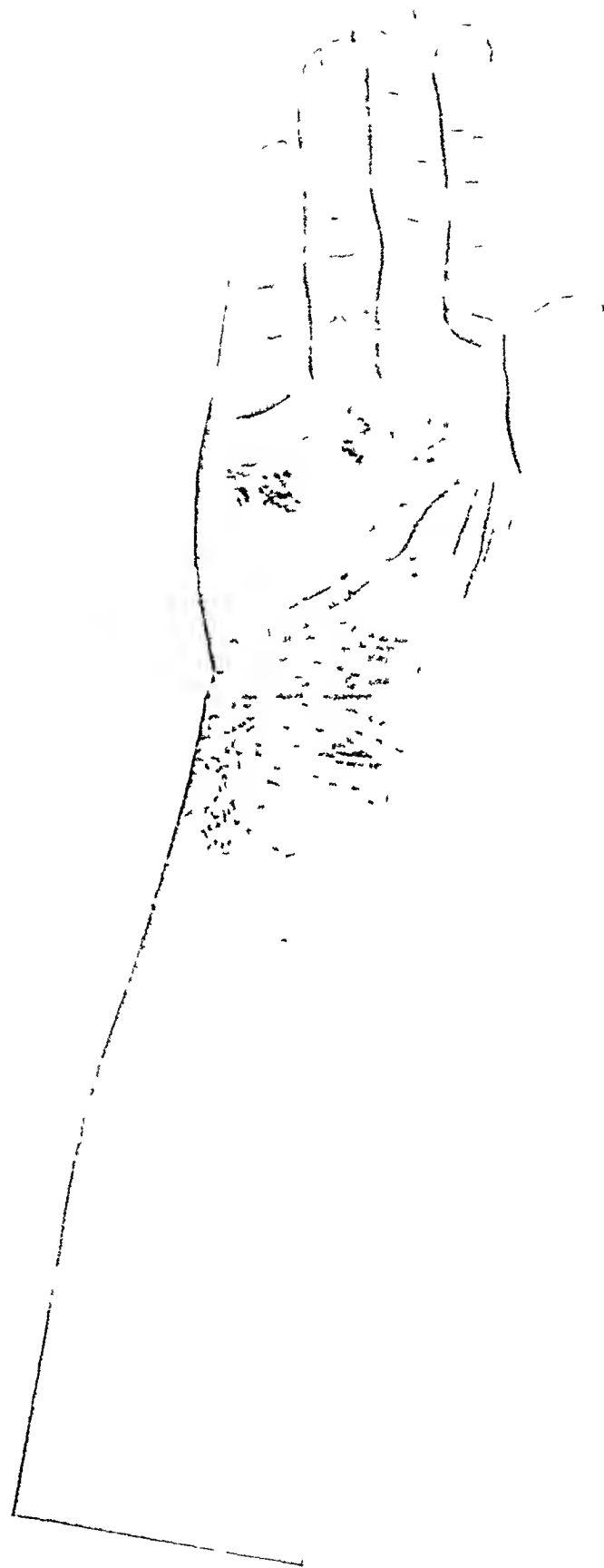


Fig 2—Dorsal view, left hand, same patient





Fig 3—Ventral view of the right hand, same patient



Fig 4—Dorsal view, right hand, same patient





Fig 5—Mucous membrane of the lips, same patient





the forearms and hands. The family history was negative. One sister had died of goiter. She had always been well until two years ago, when she had all her teeth extracted and had to live on soft, mushy foods. She could not get a good fitting plate and ate almost no meat. At Christmas, 1922, she was very nervous and felt as if she would "go to pieces." This feeling of exhaustion and weakness increased and in March, 1923, her mouth became sore, red, and hurt her when she chewed. About this time she began having seven or eight loose stools a day, and the rectum pained and burned. At this time also, the skin on the forearms, half way to the elbows, became dirty brown and scaly in appearance. The rash gradually extended to the backs of the hands and the fingers. She had never had anything like it before. All efforts to control the rash by local application failed. About two weeks after the rash appeared, the skin began to crack about the wrists. She had no headache but was confused in her mind and slow in her speech and thought. Her eyesight became blurred. She could not concentrate on whatever she was doing. The diarrhea had stopped about two weeks before the patient appeared for examination. She had lost in weight 25 pounds (11.3 kg). She stated that she had lived in the town of Mellette, S. D., for the last forty years, that she had in no way changed her diet or mode of living until after the teeth were removed two years before, when she stopped eating meat and had eaten soft foods, such as milk toast, cream of wheat, potatoes, carrots, cabbage, bread and butter, cream, cooked fruits, grape fruit, soft puddings, cake and pie.

The examination revealed a fairly well nourished woman of rather stocky build. Her color was pasty white, somewhat suggestive of myxedema, chronic interstitial nephritis, or possibly early pernicious anemia. The pupils reacted to light and in accommodation. The knee jerks were active. There was no incoordination. Her speech was slow and her mental responses sluggish. The mucous membrane of the lips and gums and inside of the mouth and the tongue were fire red (Fig. 1). There was a fine, whitish exudate, like that accompanying the spirillum of Vincent infection, over the roof of the mouth and the jaws. This was easily wiped off. In places, the mucous membrane hung down in folds. A remarkable, crusty, dirty brown pigmentation and rash was present from about the middle of the forearms downward, extending over the backs of the hands and on the proximal parts of the fingers (Figs. 2 and 3). On the inside of the wrist the skin was cracked and red in crevices. The rash had a rough, raised feel, and a branlike exudate could be rubbed off. The rest of the body was free of this skin rash, except a scaly, brownish area, the size of a dollar, over the dorsal surface of the right foot. There was a scaly, dark brown pigmentation and rash about the anus, and the mucous membrane of the rectum was red and angry looking. The rest of the physical examination was negative, except that there was some difference in the muscle strength in the extremities, the left arm and leg being stronger than the right.

The urine findings were negative except for a trace of albumin and an occasional narrow hyaline or granular cast. The blood findings showed a fairly high grade secondary anemia, hemoglobin, 65 per cent, red cells, 3,296,000, leukocytes, 6,250. Differential count: polymorphonuclears, 70 per cent, small mononuclears, 19.5 per cent, large mononuclears, 7 per cent, transitionals, 0.5 per cent, eosinophils, 2.5 per cent, myelocytes, 0.5 per cent. No nucleated reds were seen, no polychromatophilia, no basophilic stippling, no anisocytosis. The Wassermann test was negative. Blood pressure, 132 systolic, 90 diastolic. Smears from the exudate on the gums and roof of the mouth showed no spirilla of Vincent, but a long bacillus and diplococci.

A diagnosis of pellagra was made and the patient was placed on a liberal meat diet, with beef juice, and daily intravenous injections of fresh made sodium cacodylate, from 2 to 5 grains (from 0.130 to 0.324 gm) to the dose. She improved steadily but slowly. She was dismissed from Abbott Hospital on May 21, less than two months after her admission, the dermatitis and pigmentation gone, the mucous membranes free from redness and irritation, the

weakness and exhaustion almost gone, and the anemia corrected to a large degree. A letter from her in July reported no recurrence of the rash or other symptoms.

Dr. Joseph Goldberger, of the U. S. Public Health Service, the recognized authority on pellagra in this country, and Dr. John Butler of Minneapolis, examined the patient and confirmed the diagnosis of pellagra.

# STUDIES OF ACUTE INTESTINAL OBSTRUCTION

## I DIFFERENT TYPES OF OBSTRUCTION PRODUCED UNDER LOCAL ANESTHESIA

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Acute intestinal obstruction as presented in our schools and described in textbooks is often treated as a clinical entity in which there is one chain of symptoms and one type of treatment. The various etiologic factors are mentioned, but no variance of symptomatology or treatment to correspond with the diverse pathology is specified. The mortality rates are also usually classified under one general heading despite the dissimilar pathogenicity.

In a like manner, most of the experimental work of the last thirty years has disregarded the different underlying morbid conditions. The endeavor has generally been to find one specific lethal factor. Little notice has been taken of the extent or type of the lesion produced. This treatment of the subject must be fundamentally wrong. If not, how are we to explain the great differences in the physical and mental condition in acute obstruction cases seen clinically?

One patient, with an acute obstruction of six or eight *hours'* duration, appears to be in profound collapse. His face is pale and the expression anxious. The eyes are sunken, the features pinched and the skin is covered with a cold clammy sweat. The pulse is very rapid and feeble, the temperature is subnormal. The tongue is dry and parched, and the thirst is incessant. Vomiting is profuse and foul smelling, and is preceded by abdominal pain. The blood pressure has fallen to 60 or 70.

Another patient, with an obstruction of three *days'* duration, seems to be in fairly good condition. The temperature, pulse and respiration are practically normal. The patient may complain bitterly of pain and frequent vomiting but he presents none of the collapse symptoms shown by the former case. The blood pressure is normal or only slightly lowered.

In addition to this marked physical and mental contrast, these cases, when examined in the surgery or at necropsy, reveal vast differences in the underlying pathologic conditions. The former patient has an acute strangulation the latter a simple obstruction of the bowel lumen.

In reviewing a series of clinical cases, we noted that the severity of the symptoms and the pathology of the tissues involved usually ran

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parallel, and we believe, therefore, that, clinically, acute obstruction should be divided into two classes 1 Acute strangulation, those in which there is an interference with the venous, arterial and lymphatic circulation in the bowel wall and mesentery as well as complete obstruction of the intestine lumen Under this heading can be grouped volvulus, strangulated hernia, intussusception, etc Clinically, they present pictures similar to the first case described above This group totals about 80 per cent of obstruction cases 2 Acute simple obstruction, those in which there is a complete blockage of the bowel lumen only, with practically no circulatory involvement The obstruction here may be produced by gallstones, enteroliths, foreign bodies, adhesions or bands The clinical picture corresponds to the second case described This group comprises approximately 20 per cent of the total

These two classes have a different mortality rate, the process progresses more rapidly to a fatal outcome in one type than in the other, and it seems logical to conclude, therefore, that the cause of death must vary in the two types As a natural corollary to this, the treatment should be altered accordingly

The purpose of the following experiments was to ascertain whether this classification would hold true on experimentally produced obstruction, and also to determine whether the lethal factors varied in the different types

A review of the work on experimental obstruction reveals that few investigators had observed such a distinction although it had been long recognized clinically Furthermore, no worker has been able to obtain a true postoperative picture of either type In these investigations, practically all of which were made on dogs, symptoms of ileus comparable to those seen in human beings were not observed A critical examination of their methods discloses the fact that all operations were performed under ether or ether-morphin anesthesia These drugs are known to cause a general central depression and an atonic state of the intestinal musculature for from twenty-four to forty-eight hours It is during this time that all obstruction cases show their most characteristic objective signs In many strangulation cases, the subjects die within the first eight to forty hours It seems evident, therefore, that the anesthesia masks the picture

The first problem was to devise a technic by which we could produce experimentally an obstruction that would leave the animal operated on as nearly normal as possible All drugs acting on the intestine or with prolonged effect on the central nervous system had to be eliminated After considerable experimental work, it was found that excellent results could be obtained with local anesthesia by subcutaneous injection of procain and epinephrin, along the expected line of incision one half hour before operation During the operation, a large amount of the injected

solution seeps out of the tissues into the field of operation and is wiped away. The small fraction remaining in the tissues is very slowly absorbed owing to the vasoconstrictor action of epinephrin. It is rapidly oxidized in the body tissues, and therefore produces slight if any central effect. Within an hour after the injection, there is thus no complicating factor that would not be found in human obstruction cases except the small incision through the linea alba. Dogs, when operated on by this method, present a symptom complex comparable in detail, within the limits of any animal experimentation, to those exhibited by man.

#### METHODS AND TECHNIC

Dogs were used exclusively in the experimental work. Observations for normal data were made on all dogs for several days previous to operation. All experiments were performed under local anesthesia by careful aseptic methods. About from 40 to 60 c c of procain, 0.25 to 0.50 per cent and epinephrin 1:10,000 was injected about one half hour before operation. No toxic symptoms were ever manifested. The animals were strapped on a well padded operating table and were made as comfortable as possible. The surgical procedure was accomplished quickly, seldom consuming more than fifteen minutes, and with little or no trauma. All obstructions were produced by tying the intestine with a heavy cord or small rubber catheter or by clamping with aluminum clamps. Blood pressure was taken under local anesthesia on the femoral artery to avoid the complications with the vagus and sympathetic trunks which occur when the common carotid is used. A standard mercury manometer was used and tracings were recorded on a drum kymograph.

Group 1—Acute simple obstruction. To demonstrate the typical symptoms of a dog with acute simple obstruction produced under local anesthesia. In this series of twenty-one animals, simple ligation was performed at the duodenojejunal junction on nine animals, the lower jejunal on seven and the upper ileac on five. The symptoms presented at these different tie levels are practically identical. The following protocol of a dog under continuous observation presents the typical picture.

Adult male, black and white mongrel, weight 16 pounds (7.2 kg), operated on, Jan 10, 1923, time of operation fifteen minutes, off table at 5:15 p m.

January 10, 4:00 p m. Temperature 102.2 F, pulse 90, respiration 18, blood pressure 150 (systolic).

- 4:30 Operation, dog active, appears normal in every respect.
- 5:30 Vomits large amounts of bile stained partly digested food.
- 6:15 Has been very restless, gets up and lies down frequently and whines.
- 6:30 Drinks considerable water.
- 6:45 Drinks again, restless, whines some.
- 6:50 Retches ten times and vomits 50 c c of bile stained alkaline liquid containing some bile content. Yelping precedes this retching.
- 6:55 Retches severely and vomits.

- 7 05 Drinks small amount of water several times  
 7 20 Restless, head down, appears nauseated  
 7 35 Restless, retches, no vomitus  
 7 40 Respiration 20, pulse 100, temperature 102.4 F, blood pressure 155  
 7 55 Whines loud and long, drinks  
 8 00 Resting, occasional subdued whine  
 8 15 Dog up, whines loudly, vomits profusely three times, vomitus alkaline watery fluid, some mucus  
 8 18 Drinks again, is hypersensitive and apprehensive, lies down  
 8 25 Up whining, appears slightly exhausted  
 8 55 Has been resting rather quietly  
 9 00 Up, drinks, in a minute whining Vomits three times, lies down  
 9 23 Up, whines, retches, no vomitus  
 9 30 Drinks small amounts several times  
 9 35 Up howling, retches, vomits repeatedly  
 9 40 Resting quietly Temperature 102.8 F, pulse 95, respiration 20, blood pressure 155 (systolic)  
 9 55 Howls, retches and vomits profusely  
 10 00 Resting  
 10 10 Up, vomits several times small amounts with some mucus  
 10 20 Resting

From 11 00 p m the dog was placed in a cage and was not observed until 7 00 a m

January 11, 7 00 a m Dog looks somewhat haggard but is not toxic Temperature 103.1 F, pulse 95, respiration 18, blood pressure 145

From 7 00 a m to 1 00 p m, the dog drank often, vomits much less frequent but greater amounts

4 00 p m Temperature 102.6 F, pulse 90, respiration 18, blood pressure 145 The animal seems in no pain and does not vomit unless he drinks water

January 12, 2 00 p m Dog appears to be in very good condition Temperature 102.8 F, pulse 100, respiration 22, blood pressure 145 (systolic) The total vomitus today is 180 cc more than the fluid intake Vomitus is yellowish brown watery liquid, alkaline in reaction and has a slightly foul odor

January 13, 4 00 p m Temperature 103.0 F, pulse 100, respiration 22, blood pressure 140, vomitus 80 cc The animal appears weaker, weight 14.1 pounds (6.4 kg) Apparently in no pain and has vomited only a few times today

January 14, 10 10 a m The dog was given a barium sulphate meal Fluoroscopic examination reveals that the bowel above the tie is still very active Frequent peristaltic waves are seen starting in the stomach and rapidly running down to the tie at the lower end of the duodenum The duodenum which is now considerably dilated gradually fills and violent peristalsis continues for several minutes These waves are followed by a period of quiescence After a few minutes, a contraction and shortening of the entire duodenum, beginning about a half inch above the tie and quickly extending upward, forces all of the barium sulphate back into the stomach The duodenum then remains empty for several minutes, after which the above mentioned cycle is again repeated

4 00 p m Temperature 103 F, pulse 100, respiration 22, blood pressure 140 (systolic) The barium sulphate meal has been regurgitated as well as about 40 cc of bile stained fluid

January 14, 1 00 p m No vomiting today The tie has evidently cut through and the bowel reunited Eats ravenously and drinks a great deal Temperature 102.6 F, pulse 95, respiration 20, blood pressure 145 (systolic)

January 15 No vomitus Dog has had normal stool Recovery complete and uneventful

Of this series, five dogs died of peritonitis following perforation at the base of the tie. In the remaining sixteen dogs, the tie cut through in from three to six days as shown by discontinuance of vomiting and passage of stool, or evidenced by fluoroscopic examination. The only objective symptom displaying any particular variation was the degree of whining that was manifest. This is purely an individual characteristic of the different types used.

TABLE 1—*Daily Observations on Temperature, Pulse, Respirations and Blood Pressure on Dogs with Simple Obstruction with Recovery*

Dog	Weight, Pounds	Days	Average Daily			Blood Pressure (Systolic)
			Temperature	Pulse	Respiration	
2	43	1	102.4	90	18	150
		2	102.4	110	20	145
		3	102.8	104	20	140
		4	102.8	100	20	155
4	37.1	1	101.8	94	18	152
		2	102.6	100	20	145
		3	102.8	106	18	142
5	11	1	103.4	95	20	148
		2	103.8	110	20	144
		3	104.2	108	20	135
9	30	1	101.6	86	18	156
		2	102.8	88	18	140
		3	102.2	94	20	138
		4	102.3	90	16	144
10	29	1	102.2	84	16	138
		2	102.8	98	18	135
		3	103.6	106	20	138
11	15	1	102.4	86	20	160
		2	102.4	96	22	154
		3	102.6	100	20	148
		4	103.2	104	20	
15	35	1	102.7	90	16	126
		2	101.9	100	18	120
		3	103.6	104	20	110
16	31	1	102.8	88	20	144
		2	102.9	110	24	148
		3	103.1	106	22	135

This characteristic protocol and the data presented in Table 1 demonstrate that dogs with acute simple obstruction never show any symptoms of collapse although they are noticeably distressed by the violent abdominal pain and profuse vomiting. The pulse and respirations are but slightly increased, the temperature is usually normal, and the blood pressure exhibits but slight variation even after from forty-eight to ninety-six hours. The slight increase in temperature and pulse rate is probably due to the small localized peritonitis which occurs at the point of the tie and the tissue absorption from the abdominal incision, a condition often observed in control animals with an uncomplicated abdominal incision.



The seven unselected cases of acute simple obstruction due to adhesive bands, presented in Table 2, were seen by us at Emanuel Hospital during 1921. All diagnoses were verified at operation. Six patients recovered. One died following resection and end to end anastomosis and a complicating peritonitis.

TABLE 2—*Human Series of Acute Simple Obstruction Produced by Adhesion Bands\**

Patient	Age, Years	Days	On Day of Entrance			Blood Pressure		Results
			Temper- ature	Pulse	Respi- ration	Systolic	Diastolic	
Mrs B E	28	1	97	80	18	116	82	Recovered
Mrs E D B	43	7	99.8	90	20	140	92	Died after 9 days
Mrs F J	57	3	99.8	70	18			Recovered
Mrs A F	38	3	102.4	120	22	120	90	Recovered
Mrs F F	43	3	100.2	94	18	160	90	Recovered
Mrs S C B	71	3½	99.5	86	22			Recovered
Mr L	56	8	98.6	78	18	150	70	Recovered

\* All but one patient made uneventful recoveries after severance of the tissue band.

The subjoined case history demonstrates the striking similarity between clinical and experimental obstruction under local anesthesia.

#### REPORT OF CASE

*History*—Mrs E D B, aged 43, a Christian scientist, stated that the onset of her present illness began one week before entrance by a sudden attack of extremely severe colicky pain localized in the umbilical plane. The pain appeared to come in waves, increasing in severity until a climax was reached followed by a period of quiescence. She soon became nauseated and later began to vomit. Vomiting continued about every thirty minutes, with differing degrees of severity, for the next six days. The evening of entrance the condition had become more severe. At first, the vomitus was food recently eaten, followed by bile tinged liquid. On the second and third days, it was foul smelling. About three hours after the onset, the patient had had bowel movement, but there had been none since then. The temperature had been normal throughout the course. She had had no chills but complained of some cold sweating. From the first, she had been extremely bloated.

The appendix and right ovary had been removed twenty years before. The menstrual history was negative except for three questionable miscarriages. For the last year, she had complained of pain and gas distress after meals.

*Physical Examination*—The patient was a normal, well nourished individual. The pathologic condition was confined to the abdomen, which was markedly distended and tympanitic. There was little or no rigidity, but it was tender, particularly over the lower duodenum area, where a palpable mass could be outlined. Auscultation revealed violent borborygmus above the umbilical line.

*Laboratory Findings*—Leukocyte count rose from 10,750 at 5 p m to 21,200 at 9 p m, just before operation, differential polymorphonuclears, 67 per cent, small mononuclears, 12 per cent, large mononuclears, 16 per cent, transitionals, 3 per cent, eosinophils, 2 per cent. Examination of the urine revealed specific gravity 1.035, albumin, plus. The blood pressure was 140 systolic, 92 diastolic.

*Pathologic Findings*—An adhesion band completely obstructed the lower ileum with recent perforation at the base of the band. There was dilatation above the obstruction, but little or no circulatory involvement.

The foregoing clinical case clearly reveals, as do the experimental ones, that, in simple obstruction, there is but slight deviation from the normal in temperature, pulse, respiration or blood pressure. Furthermore, the symptoms are very similar, and if the obstruction is removed by cutting through or by surgical intervention, most of these patients recover. The low mortality rate is also undoubtedly due, in part at least, to the replacement of body fluids and salts by the introduction of large quantities of physiologic sodium chlorid solution and glucose after operation. The case cited in detail above, in which operation was refused until the eighth day, shows clearly that toxemia if present in these cases, plays but a very small rôle. Of course, if the integrity of the bowel is destroyed by perforation, we are dealing with a complication of a very different nature.

**Group 2—Acute strangulation.** To illustrate the symptomatology in dogs with experimentally produced acute strangulation of varying lengths of small intestine. This series includes twelve dogs. As the results are uniform, only one typical protocol will be given in detail. A more comprehensive report on this series will appear later.

Dog 28, healthy Spitz female, weight 17 pounds (7.7 kg), 9 a. m. normal, temperature 102.2 F, pulse 84, respiration 18, blood pressure 150 (systolic), operated on at 10:20 a. m., off table at 10:35 a. m.

10:20 A complete venous and lymphatic obstruction of a large segment of bowel was produced by twisting and tying off the intestine and mesentery with a small rubber catheter. The tie was not made sufficiently tight to shut off the arterial flow immediately but caused a marked venous occlusion at once.

10:35 Off table, walks around room, appears perfectly normal.

10:47 Vomits 30 cc of whitish stomach content, acid to litmus. Whines repeatedly and appears very nervous. Drinks small amount of water.

11:10 After whining and retching, vomits 40 cc of alkaline slightly bloody and bile stained fluid.

11:12 Retches and vomits a few cubic centimeters of very thick slimy mucus. Whines repeatedly.

11:19 After severe howling and retching, vomits 20 cc of blood stained alkaline fluid. This fluid has evidently come from the obstruction level.

11:26 Howls and retches, but raises no vomitus.

11:38 Howls loudly and vomits 20 cc of the usual thick frothy mucus. This fluid has the appearance of egg albumin although it does not give a reaction for albumin. It is negative for bile and shows but a slight trace of proteolytic and lipolytic enzymes.

11:50 Drinks again.

12:00 m Animal is now beginning to show definite collapse symptoms. The eyes are retracted, pupils dilated, ears and tail drooping, nose dry, thirst incessant and the extremities cold. The respirations are loud and rapid, the pulse is greatly augmented and of small volume. The gait is unsteady and animal leans heavily against the side of the cage. The entire attitude is one of extreme dejection.

12:00 m to 1:00 p. m. Frequent drinking and vomiting during this hour. The dog is rapidly becoming more dazed and whines less frequently. Collapse is more pronounced.

1:10 Whining at short intervals, drinks frequently. Temperature 101.5 F, pulse 135, respiration 38, blood pressure 80 (systolic). This doubling of the

pulse and respiratory rates, subnormal temperature and extreme fall in blood pressure indicates an already advanced case of shock

- 1 40 Retches profusely, then vomits 140 c c clear slimy mucus
- 1 45 Drinks considerable and whines Very weak Gait staggering, falls when attempt is made to lie down
- 1 56 Gets up with effort, cries, vomits 25 c c mucus Drinks again
- 1 59 Lies down, retches but raises no vomitus
- 2 03 Whines, gets up, drinks and lies down again
- 2 28 Gets up, howls, retches and vomits 50 c c of clear mucus
- 2 45 Dog resting, breathing very heavily Whines frequently
- 2 55 Temperature 100.8 F, pulse 140, respiration 40, blood pressure 70
- 3 02 Whines, drinks, retches violently and vomits 50 c c
- 3 17 Resting quietly, suddenly up, whining, drinks and then yelps
- 3 40 Retches twelve times, and finally raises 20 c c of slimy mucus
- 3 55 Yelps frequently and drinks, exhaustion more marked
- 4 11 Retches fourteen times, vomits a few cubic centimeters
- 4 25 Drinks small amount, whines, retches but raises no vomitus
- 4 47 Drinks again, two minutes later retches twenty-two times and then vomits 60 c c Temperature, 100.2 F, pulse, 240, respiration, 44, blood pressure, 60 The pulse has shown a profound increase and is of small volume The respiration has trebled its rate, and the rectal temperature is subnormal The blood pressure is very low
- 5 30 There has been a vomitus of 175 c c more and 125 c c of water has been consumed since the last period Whining is less frequent and greatly subdued
- 8 00 Consumed 140 c c of water, about 160 c c of vomitus since 5 30 Temperature, 99.2 F, pulse, 300, respiration, 63, blood pressure, 62 The animal was hardly able to stand and was insensitive to most pain The belly was opened without a local anesthetic and the belly cavity and bowel examined The gangrenous loop was immensely distended and black There was no evidence of perforation The segment was perforated with a needle, and a stream of bloody fluid ejected in a fine stream for 3 feet No evidence of pain throughout this procedure
- 8 45 Dog up, drinks, and then falls down
- 9 00 Resting in cage Retches suddenly and vomits a few cubic centimeters
- 9 15 Prone in cage Temperature, 102, Pulse, 300, respiration, 76, blood pressure, 40
- 10 00 Moribund, necropsy

All dogs in the series died in from seven to twenty-four hours In all cases, the blood pressure exhibited a conspicuous fall within six hours after the strangulation was produced Within two hours, there was always at least a doubling of the pulse rate A consistent increase in respiratory rate and usually a fall in temperature were noted within the first from eight to ten hours

These experiments represent strangulation of from 15 to 35 inches (37.5 to 87.5 cm) of small intestine, the ligature being tied in such a manner as to cause immediate and complete venous stasis These two factors, namely, the length of the segment and the completeness of venous obstruction, are extremely important, as they determine directly the degree and rapidity of onset of shock In cases in which the segments are long and there is complete venous occlusion, shock appears early and is profound When short loops are employed, it comes on slowly and is seldom very marked There are naturally all gradations between

these two extremes. It is thus evident that, in acute strangulation, the lethal factors vary in all cases. The extent of shock is directly proportionate to the length of intestine involved and the degree of venous obstruction.

The foregoing experimental group is comparable only to the most severe human cases of volvulus and extensive internal strangulation. The majority of cases seen clinically are inguinal and femoral hernia, with but a few inches of strangulated intestine and only partial venous obstruction. Furthermore, the patients are usually seen within a few hours from onset, and early surgical intervention occurs before alarming symptoms can develop. For these reasons, we were unable to obtain a sufficiently large series of clinical cases similar to our experimental type. A review of the case reports in the literature will convince one of the striking similarity between symptomatology of the experimental cases and that of the human cases.

Following is a protocol presenting the symptomatology of a dog with simple obstruction, under morphin and local anesthesia (procain), demonstrating the effect of morphin on the objective signs.

Male mongrel, weight 17 pounds (7.7 kg), operated on Jan 10, 1923, at 3 30 p m, with morphin, 1 grain.

A simple obstruction was produced by ligating the duodenum with a heavy cord. A rather large window of cellulose was sewed into the abdominal wall after the removal of part of the rectum. The bowel could be observed directly at any time on the table.

4 00 Sleeping quietly

4 30 Peristalsis can now be elicited on pinching the bowel, but there are no cramp spasms or violent waves evident.

5 00 Resting quietly

6 40 Very shallow peristaltic waves can be seen for the first time passing over about 8 cm of intestine above the tie. Dog whines while this occurs.

7 00 Whines occasionally

7 30 More or less repeated peristalsis, rather rapid, can now be seen running over the visible segment of bowel. The waves stop a centimeter or two above the obstruction. Occasional whimper during activity of the waves.

8 30 Almost continuous peristalsis, quite vigorous, is present over the visible segment. The waves follow each other at intervals of about from two to four seconds. Repeated antiperistalsis can now be seen beginning above the obstruction and passing over the entire segment. These waves are not preceded by the true inhibitory phase but appear more as a massive contraction originating just above the obstruction.

8 40 Dog awake. Tries to get up.

9 00 Bowel is more active.

9 10 Dog whines, struggles to get up, segment above tie is in spasm.

9 30 to 11 00 Occasional whines. Dog has not vomited while under observation.

11 00 p m to 9 00 a m Placed in cage and not observed. Peristalsis now present above and below tie. Animal in good condition. Killed for tissue examination.

These observations clearly demonstrate that morphin inhibits peristalsis for a period of from three to six hours and thus prevents the appearance of the usual symptom complex. If it is used in conjunction with ether, the effects are still more prolonged.

#### COMMENT

So far as we were able to ascertain, no previous work of this nature has ever been attempted under local anesthesia. The method has its difficulties, requires patience and necessitates minimum manipulation. However, these very factors render the experimental states as nearly as possible like those that occur under normal conditions. Further, we have been able to reproduce, in these experimental animals, symptom complexes which simulate and parallel the clinical entities. It seems logical, therefore, that the results and deductions in a large measure should be applicable to human cases.

The division of acute intestinal obstruction into acute simple obstruction and acute strangulation appears to be amply proved by this experimental work. In the former, we are dealing with obstruction of the lumen of the intestine without circulatory involvement of much consequence. In the latter, there is segmental obstruction plus extensive vascular derangement.

The rapid fall in blood pressure, the great increase in pulse and respiratory rates, the subnormal temperature and the certain speedy death in acute strangulation when compared with the normal temperature, pulse, respiration and blood pressure in acute simple obstruction indicate that the underlying lethal factors must be different in each type.

In acute strangulation, we are dealing primarily with a shock complex, in which toxemia, dehydration and chlorid loss play but little part. In simple obstruction, shock is not present, and toxemia per se is but a slight factor, if present at all, death instead being due to perforation and peritonitis or, in uncomplicated cases, to inanition, dehydration and chlorid deficiency. These differences in pathology and mortality demand special operative and postsurgical treatment for each type.

#### CONCLUSIONS

1 Intestinal obstruction as produced experimentally under local anesthesia in dogs closely resembles the human symptom complexes.

2 Experimental acute intestinal obstruction can be classed under two general headings, (1) acute simple obstruction and (2) acute strangulation.

3 The pathology of these two groups is distinctly separable and the lethal factors are different.

4 The symptom complexes of the two types are also very different. Acute simple obstruction shows relatively slight variations in temperature, pulse, respiration and blood pressure, while acute strangulation causes profound changes in these physiologic indicators.

5 Uncomplicated blood pressure observations on dogs following bowel obstruction, can be secured from the femoral artery under local anesthesia.

6 Ether and morphin must be eliminated in experimental studies of the acute symptomatology of intestinal obstruction.

# THE QUANTITATIVE AMOUNT OF LIPOID MATERIAL IN THE KIDNEY AND ITS RELATION TO THE FUNCTIONAL RESPONSE IN EXPERI- MENTAL NEPHRITIS \*

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The presence of various forms of fatty materials, i e, lipoids, in the kidney in acute nephritis is one of the most important histologic findings. The relation of these substances to the altered functions of the kidney and to the latter stages of chronic nephritis is not well known. An understanding of these relations would serve as stepping stones toward the solution of many problems which are of vital clinical importance.

An experimental study of lipid changes in nephritis in animals offers an approach which at present is not possible in dealing with early nephritis in man. It is only in exceptional instances that gross material can be obtained from a patient with early nephritis since he either recovers or progresses on to a chronic condition.

In producing kidney changes we have used uranium nitrate because the histology of this type of experimental nephritis has received a great amount of study and is well understood <sup>1</sup>. Uranium nitrate has a particular action on renal epithelium, and the degree of nephritis it produces may be controlled by the dosage. The resulting nephritis simulates early nephritis in man.

Lipoid material in the kidney may be studied in two ways (1) microscopically by the use of special stains, (2) chemically by means of quantitative extraction. MacNider,<sup>2</sup> using the first method, studied the amount and distribution of stainable lipid material in the renal epithelium of dogs, and demonstrated microscopically the degree of fatty changes. In addition to the first method, we have used the second and have recorded the percentage of fatty change in the kidney and

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\*From the laboratories of the Potter Memorial Clinic and the Santa Barbara Cottage Hospital.

1 MacNider, W de B. A Functional and Pathological Study of Chronic Nephropathy Induced in the Dog by Uranium Nitrate, *J Exper Med* **29** 513 (May) 1919.

2 MacNider, W de B. A Preliminary Paper on the Relation Between the Amount of Stainable Lipoid Material in the Renal Epithelium and the Susceptibility of the Kidney to the Toxic Effect of the General Anesthetics, *J Pharmacol & Exper Therap* **17** 289 (May) 1921.

liver. We have attempted to correlate the functional response of the kidney with the actual amount of lipid material and with the histologic pictures.

We have also contrasted the extent of the fatty change in the kidney and liver, and have endeavored to determine in which organ these changes occur first.

*Material*—Young rabbits, each weighing about 4 pounds (1,814 gm) were used.

*Method*—The rabbits were divided into five groups.

*Group 1*—Seven control animals were in this group.

*Group 2*—The rabbits in this group were given 4 mg of uranium nitrate subcutaneously and then killed at progressively increasing intervals, twelve, eighteen, twenty-four, forty-eight, seventy-two and ninety-six hours from the time of inoculation.

*Group 3*—The procedure in this group was the same as that outlined for Group 2, excepting that the experiment was followed through to the fifteenth day.

*Group 4*—These rabbits were given 4 mg of uranium nitrate subcutaneously, and immediately after the injection were given 25 cc of 3 per cent sodium carbonate solution intravenously. They were then killed at the stated hours following the injection.

*Group 5*—Seven rabbits were given four weekly doses of uranium nitrate. They were then allowed to rest for two weeks. In this manner a well marked subacute nephritis was produced. At the end of six weeks they were treated as the rabbits in Group 1.

The kidney function of each animal was studied by means of a phthalein test, by a chemical and microscopic examination of the urine and by a determination of the nonprotein nitrogen, the urea nitrogen and the carbon dioxide of the blood. These tests were repeated just before each animal was killed. Then portions of the kidneys and of the liver were extracted with ether. The technic of this method was as follows. A kidney was taken from the animal immediately after its death and weighed. It was chopped up finely and ground in a mortar with gypsum. The ground tissue, together with the gypsum, was put into an extracting thimble, the thimble placed in a Soxhlet apparatus and covered with a liberal quantity of anhydrous ether. Extraction was then carried on over an electric plate for ten hours. Following this, the excess of ether was evaporated from the flask containing the extracted fat and the flask placed in a drying chamber for twenty-four hours. The flask was then weighed carefully, and the exact amount of lipid material ascertained by subtracting the weight of the empty flask from the weight of the flask when it contained



the lipid The amount of lipid was recorded as the percentage of the total weight of the organ Two separate determinations were made from each kidney and liver and an average of the two readings recorded

Frozen sections of the kidney and liver were made and stained for fat, using Herxheimer's <sup>3</sup> technic Other sections, cut in paraffin, were stained with hematoxylin and eosin

The nonprotein nitrogen and the urea nitrogen were determined by the methods of Folin and Wu <sup>4</sup> The carbon dioxide was determined by the method of Van Slyke <sup>5</sup> It is stated as the capacity of the blood serum for CO<sub>2</sub> In making the phthalein determinations, each rabbit was given 75 c c of water by stomach tube One cubic centimeter of the dye was then injected subcutaneously The readings were made two hours after the urine in the bladder had been expressed by massage

Tables 1, 2, 3, 4 and 5 give the data obtained from the corresponding groups of animals

TABLE 1—Control Animals in Group 1

Animal	CO <sub>2</sub> , Percentage by Volume	Non protein Nitrogen Mg	Uranium Nitrate, Mg	Phthalein Percentage	Urine	Percentage of Lipid	
						In Kidney	In Liver
1	65	38.4	20.7	75	Negative	3.63	3.04
2	59	44.2	27.0	68	Negative	3.65	3.46
3	55	36.2	22.0	64	Negative	3.10	3.18
4	68	52.4	32.2	78	Negative	3.19	3.10
5	54	48.0	28.7	56	Negative	3.40	3.80
6	52	34.0	16.4	58	Negative	3.60	3.80
Average						3.43	3.42

## RESULTS

The phthalein output in a series of seven control animals, and in the twenty-eight animals at the beginning of the experiments varied from 46 to 85 per cent The carbon dioxide of the blood serum ranged from 52 to 71 per cent by volume The nonprotein nitrogen of the blood varied from 36 to 65 mg per hundred cubic centimeters of blood The urea nitrogen ranged from 16 to 30 mg per hundred cubic centimeters The urine did not contain pathologic constituents either on chemical or microscopic examination

Stainable lipid was not found in frozen sections of the kidneys of the control animals The liver, however, contained fine droplets in the cells throughout the liver lobule

3 Method given by MacNider in Footnote 2, page 292

4 Folin, O., and Wu, H. A System of Blood Analysis, J Biol Chem 38 81 (May) 1919

5 Van Slyke, D. D., and Cullen, G. E. The Bicarbonate Concentration of the Blood Plasma, Its Significance, and Its Determination as a Measure for Acidosis, J Biol Chem 30 289 (June) 1917

Twenty-four hours following an injection of 4 mg of uranium nitrate into an animal, five droplets of lipid were found in the kidney, in the cells lining the loops of Henle and the proximal convoluted tubules. Fine droplets were present in the cells throughout the liver lobule, in an amount considerably in excess of the controls.

The kidneys from an animal killed forty-eight hours following a uranium nitrate intoxication, contained large droplets of lipid in the cells lining the loops of Henle, while the cells lining both the proximal and distal convoluted tubules contained fine lipid droplets which made them stand out sharply. These droplets occurred throughout the cell in contrast to the peripheral location of the droplets in the animal in which the intoxication was of twenty-four hours standing. The liver cells contained an increased number of small lipid droplets, especially about the periphery of the lobule.

At the end of seventy-two hours, ninety-six hours and one hundred and twenty hours, both fine and large droplets of lipid were present in the kidney and liver, in the areas indicated, but apparently in decreased and varying amounts. This may have been due in part to other microscopic evidences of injury becoming more pronounced. These microscopic variations led us to extract the lipid material from these tissues by chemical methods, in order to determine the exact percentage of lipid material present at the various periods.

The lipid material in the kidneys of seven control animals varied from 3.10 to 3.66 per cent, with an average of 3.43 per cent. The percentage of lipid in the livers of these animals varied from 3.04 to 3.80, with an average of 3.42 per cent.

In Table 2 it will be noted that twelve hours following an injection of 4 mg of uranium nitrate into a normal animal, a marked drop in the carbon dioxide of the blood serum resulted. This evidence of acidosis occurred with regularity. At this time there was no appreciable change in the nonprotein nitrogen and urea nitrogen of the blood. The urine showed a faint trace of albumin, but acetone, diacetic acid and reducing substances were absent. The phthalein output was not altered. The amount of lipid material extracted from the kidney was 3.33 per cent of its total weight, and from the liver, 3.89 per cent. These figures are little changed from the average normal readings of 3.43 per cent and 3.42 per cent for the kidney and liver respectively.

Eighteen hours following the injection of a similar amount of uranium nitrate into the second animal of the series an appreciable rise in the nonprotein nitrogen and urea nitrogen of the blood occurred. The carbon dioxide of the blood serum had fallen from 66.1 to 40.4 per cent by volume. The phthalein output was reduced from 54 per cent to 45 per cent in two hours. The urine had a heavy trace of albumin with an occasional hyaline cast. The lipid material of the

kidney and of the liver had increased to 3.56 per cent and 5.41 per cent, respectively

Twenty-four hours following the uranium injection into animal number 3 of the series, the nonprotein nitrogen and urea nitrogen were increased to 78 and 48 mg, respectively. The carbon dioxide of the blood fell from 63.4 to 40 per cent by volume. The two hour phthalein was reduced from 65 to 35 per cent and the urine contained albumin, hyaline casts and a trace of acetone. The total lipid of the kidney had increased to 3.78 per cent. The total lipid of the liver was 3.85 per cent.

TABLE 2—*Normal Animals in Group 2*

Animal	Amount Uranium Nitrate, Mg	CO <sub>2</sub> , Percent age by Volume	Non protein Nitrogen, Mg	Ura nium Nitrate, Mg	Phtha lein, Per centage	Urine	Percentage Lipoid	
							In Kidney	In Liver
1 Normal 12 hr fol Uran	4	57.6 31.8	45.6 46.5	18.9 26.1	80 85	Negative Albumin, faint trace	3.33	3.89
2 Normal 18 hr fol Uran	4	66.1 40.0	58.0 65.2	25.6 30.2	54 45	Negative Albumin, faint trace	3.56	5.41
3 Normal 24 hr fol Uran	4	63.4 40.4	50.4 78.0	15.0 48.0	65 35	Negative Albumin, casts, trace acetone	3.78	3.85
4 Normal 48 hr fol Uran	4	59.5 39.0	50.0 171.4	24.0 72.0	45	Negative Albumin, casts, acetone diacetic acid	3.17	3.66
5 Normal 72 hr fol Uran	4	60.4 44.8	65.4 250.0	28.3 111.0	65	Negative Albumin, casts, acetone, diacetic acid, reducing sub	2.23	3.48
6 Normal 96 hr fol Uran	4	59.5 38.5	60.0 68.2	27.2 31.7	58 19	Negative Albumin, casts, acetone, diacetic acid, reducing sub	2.48	3.46

Forty-eight hours following the uranium injection into animal number 4, the carbon dioxide was reduced from 59.5 to 39 per cent by volume. The nonprotein nitrogen had increased from 50.4 to 171.4 mg and the urea nitrogen from 24 to 72 mg. The final phthalein determination in this instance was not made. The lipid material in both the kidney and the liver was decreased to 3.17 per cent and 3.66 per cent, respectively.

The carbon dioxide of the blood in animal number 5 that was killed seventy-two hours following the intoxication, had decreased from 60.4 to 44.8 per cent by volume. The nonprotein nitrogen and the urea nitrogen of the blood had increased from 65.4 and 28.4 to 250 and 111 mg per hundred cubic centimeters of blood. The phthalein was lost but the urine contained albumin, hyaline and granular casts, acetone

and diacetic acid and a reducing substance. The total lipid material of the kidney was decreased to 2.23 per cent and of the liver to 3.48 per cent.

Animal number 6 of the series, killed ninety-six hours following its intoxication had a decrease in the carbon dioxide of the blood serum from 59.3 to 38.5 per cent by volume. The nonprotein nitrogen and the urea nitrogen at the outset were 60 and 27.2 mg and had changed to 68.2 and 31.7 mg per hundred cubic centimeters of blood. The

TABLE 3—*Normal Animals of Group 3*

Animal	Amount Uranium Nitrate, Mg	CO <sub>2</sub> , Percent- age by Volume	Non- protein Nitrogen, Mg	Ura- num Nitrate, Mg	Phthal- ein, Per- centage	Urine	Percentage Lipoid	
							In Kidney	In Liver
1 Normal 6 hr fol Uran	4	60.0 49.9	58.8 53.0	30.0 29.0	60 65	Negative Negative	4.2	3.22
2 Normal 12 hr fol Uran	4	70.0 55.0	51.0 57.5	24.0 22.4	52 40	Negative Albumin faint trace	4.22	
3 Normal 18 hr fol Uran	4	64.4 40.0	58.8 57.6	33.0 34.0	60 20	Negative Albumin, casts	7.3	3.76
4 Normal 24 hr fol Uran	4	49.9 32.2	49.4 58.8	26.6 42.7	57 30	Negative Albumin, casts		4.68
5 Normal 48 hr fol Uran	4	52.4 29.0	52.8 60.0	38.0 41.9	70 10	Negative Albumin, casts, acetone diacetic acid, reducing sub	5.77	2.85
6 Normal 72 hr fol Uran	4	53.8 34.5	58.2 153.57	32.0 128.57	54 24	Negative Albumin, casts, acetone diacetic acid	1.36	1.30
7 Normal 168 hr fol Uran	4	58.0 17.7	60.0 546.0	35.7 500.0	55 40	Negative Albumin, casts, acetone, diacetic acid, reducing sub	1.805	2.70
8 Normal 360 hr fol Uran (15 days)	4	60.5 59.0	44.4 46.87	26.7 39.47	60 44	Negative Albumin, trace few hyaline casts	2.252	2.21

two hour phthalein output had fallen from 58 per cent to 19 per cent. The urine contained the same abnormal contents as noted in animal number 5. The total lipid material of the kidney was 2.48 per cent and of the liver 3.45 per cent.

Series number 3 differed from series number 2 in that the determinations started at six hours following the injection of uranium and were also made on the seventh and fifteen days. By the seventh day the nonprotein nitrogen and the urea nitrogen of the blood were still high 153 and 128 mg. The carbon dioxide was 17.7 per cent by volume. The phthalein output was decreased from 55 per cent to 40 per cent. Albumin and occasional hyaline casts were still present in the urine.

The most interesting findings were the very much decreased amounts of lipid material. On the seventh day the total lipid of the kidney was 1.805 per cent and of the liver 2.70 per cent. On the fifteenth day the lipid of the kidney was 2.25 per cent and of the liver 2.21 per cent. These figures were lower than any others that we had obtained.

The data in Table 4 were obtained from animals given 25 c.c. of 3 per cent sodium carbonate solution at the time of the uranium injection. It will be noted that the urine did not present the marked

TABLE 4—*Sodium Carbonate Solution Given at Time of Uranium Nitrate Injection to Rabbits in Group 4*

Animal	Amount Uranium Nitrate, Mg	CO <sub>2</sub> , Percent- age by Volume	Non- protein Nitrogen, Mg	Ura- nium Nitrate, Mg	Phtha- lein, Per- centage	Urine	Percentage Lipoid	
							In Kidney	In Liver
1 Normal 6 hr fol Uran	4	71.0 69.1	39.7 42.63	18.27 16.79	72 65	Negative Negative	3.2	3.0
2 Normal 12 hr fol Uran	4	48.8 50.3	41.1 34.5	17.64 25.42	60 44	Negative Albumin, trace	3.71	7.2
3 Normal 18 hr fol Uran	4	66.4 69.3	40.2 40.0	18.0 23.08	58 48	Negative Albumin trace	3.84	3.80
4 Normal 24 hr fol Uran	4	58.8 52.0	36.6 26.6	16.6 20.0	64 47	Negative Albumin occurs casts	5.32	4.65
5 Normal 48 hr fol Uran	4	59.6 22.6	36.32 51.0	21.66 27.3	68 40	Negative Albumin, casts	3.51	4.34
6 Normal 72 hr fol Uran	4	52.2 22.3	50.4 222.0	19.9 167.0	62 22	Negative Albumin casts, acetone diacetic acid	2.44	3.20
7 Normal 96 hr fol Uran	4	50.0 35.3	54.2 250.0	17.9 147.5	49 18	Negative Albumin casts, acetone, diacetic acid	2.48	3.67

changes that were observed in Tables 2 and 3. Traces of albumin were present, but acetone and diacetic acid were only found at the seventy-two and ninety-six hour periods. The phthalein output was reduced. The carbon dioxide of the blood was practically unaltered in the six, twelve, eighteen, and twenty-four hour experiments. The increase in the nonprotein nitrogen and urea nitrogen of the blood was also delayed, but marked retention occurred in the animals of the seventy-two and ninety-six hour period. The variation in the total amount of lipid material followed approximately the same curve as in the former series but greater variation was obtained. The decrease in the amount of lipid material at seventy-two and ninety-six hours was marked, and reached 2.44 per cent and 2.48 per cent for the kidney and 3.20 per cent and 3.68 per cent for the liver.

Table 5 records the findings in a group of animals in which a subacute nephritis had been produced by four weekly injections of uranium. After a two weeks rest a final injection of 4 mg of uranium was given and the experiments concluded twelve hours, eighteen hours, twenty-four hours etc. later as in the previous series. The urine of these animals contained faint traces of albumin only. Other evidences of pathology such as acetone, diacetic acid and reducing substances were absent. The phthalein excretions of the whole were somewhat reduced ranging from 60 per cent to 32 per cent. Following the final injection of uranium the phthalein output was again reduced, the lowest

TABLE 5—*Subacute Nephritis on Which an Acute Nephritis Was Superimposed in Rabbits of Group 5*

Animal	Amount Uranium Nitrate, Mg	CO <sub>2</sub> , Percent- age by Volume	Non- protein Nitrogen, Mg	Ura- nium Nitrate, Mg	Phtha- lein, Per- centage	Urine	Percentage Lipoid	
							In Kidney	In Liver
1 Subacute	16	50.5	50.0	25.8	50	Trace albumin	3.03	3.21
2 Subacute 12 hr fol Uran	20	48.0 50.0	58.25 72.28	24.7 37.49	60 45	Trace albumin	2.22	3.55
3 Subacute 18 hr fol Uran	20	53.7 58.0	68.1 54.5	41.6 20.3	38 42	Trace albumin	2.87	3.27
4 Subacute 24 hr fol Uran	20	53.8 50.0	51.6 51.7	28.03 20.09	32 67	Albumin	3.05	3.74
5 Subacute 48 hr fol Uran	20	57.6 49.0	62.5 48.04	27.2 24.0	45 35	Albumin	3.71	4.07
6 Subacute 72 hr fol Uran	20	57.0 51.9	47.2 51.2	30.9 28.3	48 33	Albumin	3.15	3.52
7 Subacute 96 hr fol Uran	20	56.7 54.0	70.8 56.07	42.89 32.9	38 25	Albumin	2.87	3.35

reading being 25 per cent in the ninety-six hour animal. In this animal the total lipoid material was lower than in the other animals of the series. The nonprotein nitrogen and the urea nitrogen of the blood were slightly increased as a result of the repeated uranium injections, but following the final injection there was very little change and in three instances (the eighteen, forty-eight and ninety-six hour animals) there was a slight decrease in the amount of these substances. This is easily explained. Following repeated injections of uranium an animal develops a tolerance for this intoxication and increasingly larger amounts must be given to produce marked results.<sup>6</sup> Since the final dose in this series was not larger than the former doses that had been given to produce the subacute nephritis the intoxication incident to the final injection was minimal. The degree of acidosis as determined by the carbon dioxide of the blood serum bears this out. Before the

6 Nuzum F. R. and Rothschild L. L. Experimental Uranium Nephritis, a Chemical and Pathologic Study, Arch. Int. Med. **31**: 894 (June) 1923.

final injection the carbon dioxid varied from 48 to 57.6 volumes per cent, whereas the readings following the final injection varied from 49 to 55.7 volumes per cent. The amounts of lipid material in the kidney and liver presented less variation than in the other experiments. The lipid in the control animal of this series was practically the same as in normal animals, 3.03 per cent and 3.21 per cent for the kidney and liver respectively. In the twelve and eighteen hour animals the amounts of lipid in the kidney were recorded as 2.22 per cent and 2.87 per cent, which is considerably lower than the other animals of the series. However, the increase in the twenty-four and forty-eight hour animals and the decrease after the forty-eight hour period followed the curves obtained in the other series. The increase in the lipid material of the liver reached a maximum of 4.07 per cent at the forty-eight hour period. This curve follows closely that of the change in the amount of lipid in the kidney.

#### COMMENT

Lipoid material in the epithelial cells lining the convoluted tubules and the limbs of Henle of the kidney and the parenchymal cells of the liver lobule is demonstrated with fat stains following uranium intoxication. Whether this material represents an infiltration or is a degeneration of the protoplasm of the individual cell, is a matter that has occasioned much discussion. Fatty degeneration of the cell protoplasm was perhaps best attacked by Rosenfeld.<sup>7</sup> He found that if an animal rendered fat free by starvation was fed tallow and then poisoned, the fat depots yielded the tallow to the degenerated organs. Whereas, if an animal was rendered fat free by starvation and then poisoned, degeneration could not be demonstrated. Similar observations have been made in starved human beings by Lebedeff.<sup>8</sup> Fischler<sup>9</sup> carried soap solution through excised kidneys and obtained in this way a picture of fat degeneration. Lusk<sup>10</sup> and his pupils observed these infiltrative changes in phosphorus poisoning, and interpreted them as an attempt on the part of injured cells to keep themselves alive.

But in spite of these and similar observations, pathologists have always felt that fatty infiltration does not explain the morphologic cell changes. It has been found that Rosenfeld's observations have notable exceptions and that the total fat content of a fatty organ is not always

<sup>7</sup> Rosenfeld, F. Gibt es eine fettige Degeneration? Verhandl. d. Kongressinn. Med., 1897.

<sup>8</sup> Lebedeff. Ueber Fettansatz in Thierkörper, Arch. f. d. ges. Physiol. **31** 11, 1883.

<sup>9</sup> Fischler. Ueber Experimentell erzeugte Fettsynthese, etc., Virchows Arch. f. Path. Anat. **174** 514 1903.

<sup>10</sup> Lusk. Metabolism in Phosphorus Poison, Am. J. Physiol. **19** 109, 1907.

increased but is occasionally actually diminished in weight. Work which has been done on the nature of autolysis has been particularly helpful in deciding that the protoplasm of cells may actually undergo fatty degeneration. Both in autolytic changes, and in the process of parenchymatous degeneration fine granules make their appearance within the cells<sup>11</sup>. These fine dust like particles fuse to form larger dioplets and finally the entire cell may be filled. These substances differ in two ways from ordinary neutral fat<sup>12</sup>. Physically, they give double refraction of polarized light. Chemically, their decomposition often results in the formation of glycerin phosphoric acid. Virchow called these substances "myelins". More recent investigations have shown that myelins include such substances as lecithin, protagon and cholesterol<sup>13</sup>. These were termed lipoids by Overton. They occur in animal cells in abundance and their decomposition bodies occur in traces in the urine. These decomposition bodies, on further breaking down may yield neutral fat (Oertel)<sup>14</sup>.

Studies of this nature have fairly demonstrated not only that fatty degeneration of cell protoplasm occurs, but that fatty infiltration and fatty degeneration are intricately related and doubtless often occur together, and diminished alkalinity of the blood which occurs in nephritis is an added factor in affecting these degenerative changes<sup>15</sup>.

The presence of lipid material in the kidneys and liver, following uranium intoxication, may thus be ascribed both to fatty infiltration and degeneration. Whether one process or the other is especially responsible for the presence of lipid material within the secreting cells of the kidney is of less import than the relation of these substances, when present, to ability of the kidney to function.

We have found that the maximum increase of stainable lipid, following a uranium intoxication, occurs within twenty-four hours in the kidneys and livers of animals that were previously normal. In animals in which a subacute nephritis had been established by repeated uranium injections, a maximum increase of lipid in tissue organs occurred in forty-eight hours. After this there is a diminution in the amount of this material, this diminution continuing until the fifteenth day in one of our experiments (Charts 1 to 4).

Both the initial increase and the succeeding decrease in the amount of lipid material were demonstrated much more satisfactorily by the

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11 Waldvogel. Autolyse und fettige Degeneration, Virchows Arch f Path Anat **175** 1, 1904

12 Oertel, H. The Anatomical Histologic Processes of Bright's Disease, Philadelphia, W. B. Saunders Company, 1910, p. 118

13 Aschoff. Beitr. z path Anat u z allg Path **47** 7, 1911

14 Oertel and Mandel. New York University Bull. M. Sc. **1** 165, 1901

15 Oertel, H. The Anatomical Histologic Processes of Bright's Disease, Philadelphia, W. B. Saunders Company, 1910, p. 126



extraction method than by the staining technic. The former gave data which we have plotted as curves, whereas the staining method gave variable results and at best was a matter of estimate.

In MacNider's<sup>16</sup> hands the staining technic was more successful than in ours. Using dogs, he demonstrated a microscopic increase in the amount of stainable lipid as early as six hours after the uranium intoxication. At twelve hours the amount of lipid material was increased, and at twenty-four hours there was a still greater increase. At the end of forty-eight hours he found little if any change in the amount of lipid.

The decrease in the amount of lipid material after the twenty-four to forty-eight hour period is undoubtedly due to retrograde processes.

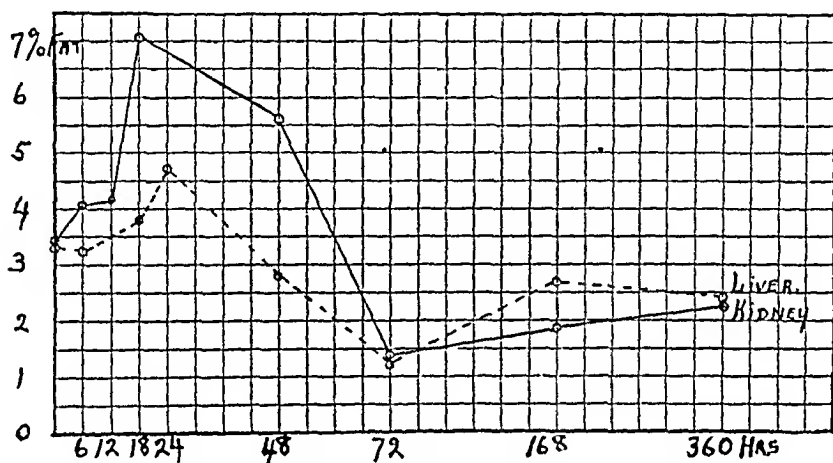


Chart 1—The percentage of lipid material in the kidney and liver at stated periods, following the onset of an acute nephritis

that follow the lipid change. These processes are evident both in frozen sections stained with scarlet red and in paraffin sections stained with hematoxylin and eosin. The endothelial cells lining the convoluted tubules become so swollen within the forty-eight hour period that they obliterated the lumen of the tubule. By this time vacuolization and necrosis are especially advanced in the endothelial cells of the convoluted tubules. The same degenerative processes are present in the liver, the cells at the periphery of the lobule being affected most severely.

The total amount of extractable lipid, as determined in our control animals, was practically the same in the kidney, 3.43 per cent, as in the liver, 3.42 per cent. In one series of normal animals (Chart 1), the increase in the lipid material in the kidney occurred somewhat earlier

<sup>16</sup> MacNider, W. de B. Concerning the Amount and Distribution of Stainable Lipid Material in Renal Epithelium in Normal and Acutely Nephropathic Animals, with Observations on Functional Responses of the Kidney, *Proc Soc Exper Biol & Med* **19** 222, 1922.

and to a greater degree than in the liver. In the second series of normal animals (Chart 2), in the bicarbonate group (Chart 3) and the subacute nephritis group (Chart 4) the reverse was true. However, in view of the close similarity of the curves depicting these changes, we feel that little significance can be attributed to the somewhat earlier and more marked changes observed in the liver in three of the four groups of animals.

The functional response of the kidney following the uranium intoxications, demonstrates that the lipid changes occur before the functional response is altered. At the six hour period the functional response is still unaltered whereas a lipid change is demonstrable in both kidney and liver. At the twelve hour period the lipid change is very evident, while the phthalein response of the kidney may still be normal and the nonprotein nitrogen and urea nitrogen of the blood remain unaltered.

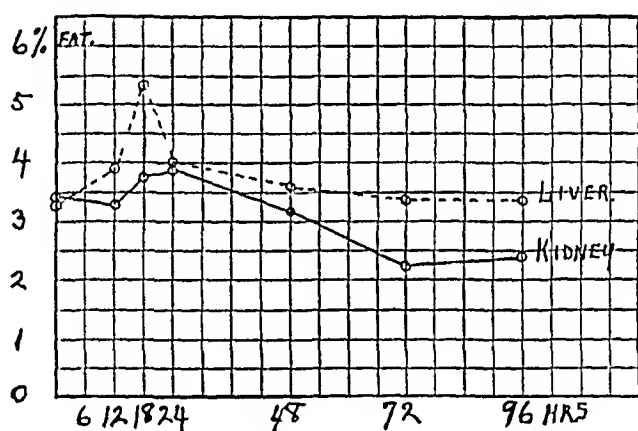


Chart 2—The per cent of lipid material in the kidney and liver in a second group of animals following the onset of an acute nephritis. The per cent of lipid in the liver is somewhat increased over that found in the kidney.

At this time, however, there is usually a decrease in the carbon dioxide and the urine may contain a trace of albumin. At the eighteen hour period, the lipid is still further increased in amount. The nonprotein nitrogen and urea nitrogen of the blood are increased, the phthalein is further decreased, the carbon dioxide is lowered and the urine contains albumin and an occasional cast. At the twenty-four hour period the function of the kidney is further depressed. This depression increases with regularity up to from seventy-two to ninety-six hours (following a 4 mg. injection into a No. 4 rabbit), at which time the phthalein may be as low as 10 per cent, the nonprotein nitrogen and urea nitrogen as high as 250 and 111 mg. per hundred cubic centimeters of blood, respectively, and the carbon dioxide 17.7 per cent by volume. The urine now contains numerous hyaline and granular casts, often acetone, diacetic acid and a reducing substance. At the time when the kidney is carrying on its work with greatest difficulty, the lipid material (as determined

by extraction), is lower than at any other time. Further degenerative processes have already been suggested as responsible for this. Following a single subcutaneous injection of 4 mg of uranium nitrate the kidney function returns to normal within from twelve to fifteen days. The lipid content, however, was still well below its normal level at fifteen days.

The protective action of sodium carbonate solution in uranium intoxication has been demonstrated by MacNider. He believes that the toxicity of the metal is associated with its ability to produce organic acids and that the carbonate lessens the toxicity by delaying and lessen-

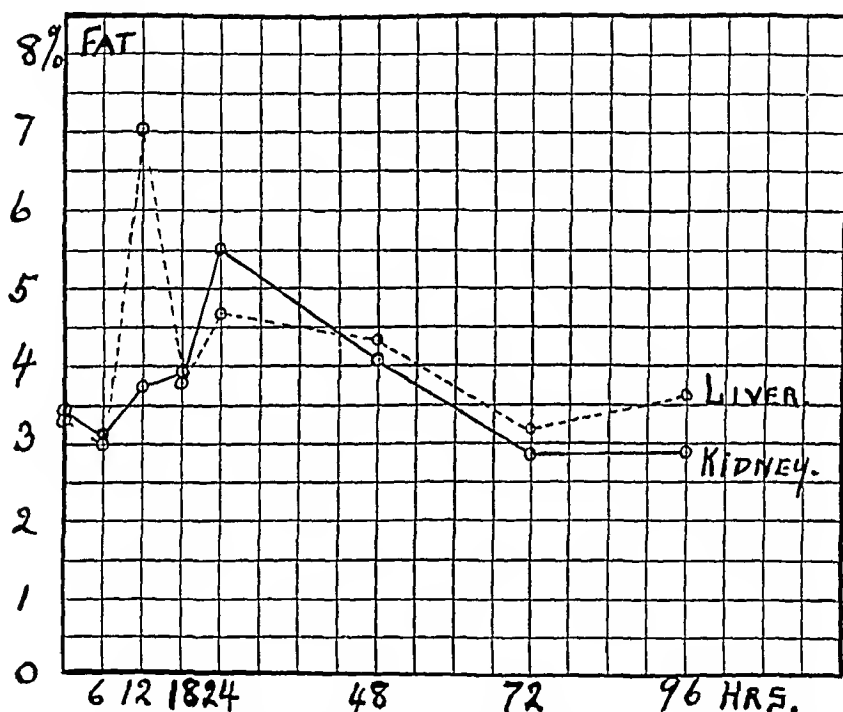


Chart 3—The lipid changes in the kidney and liver at different periods, following the onset of an acute nephritis. The nephritis was induced by uranium nitrate with a protecting dose of sodium carbonate at the time of injection of the uranium.

ing the formation of these acids. In the series of animals in which we gave sodium carbonate at the time of the uranium intoxication this protective action was well demonstrated. The depression of the kidney function was materially delayed. The nonprotein nitrogen, the urea nitrogen and the carbon dioxide of the blood were little disturbed for the first forty-eight hours of the experiments. The phthalein output was somewhat reduced and the urine contained traces of albumin. At the seventy-two and ninety-six hour periods, however, functional disturbance was very evident. The alterations in the amounts of extractable lipid material in both kidney and liver, nevertheless follow curves quite

comparable with the groups of animals in which no protecting carbonate solution was given. The maximum amounts of extractable material were obtained at the twenty-four hour period, the minimum amounts at the seventy-two hour period, and at the end of ninety-six hours a slight increase in the amount of lipid had occurred. Thus, while the toxic action of the uranium was definitely delayed, had larger amounts of carbonate solution been used, the early minor disturbance and the late marked kidney disturbance might have been avoided and lipid change in the kidney and liver might not have occurred.

As a further means of studying the relationship of the lipid content of the kidney to its functional response, we repeated our experiments on a group of animals in which a subacute nephritis had been established

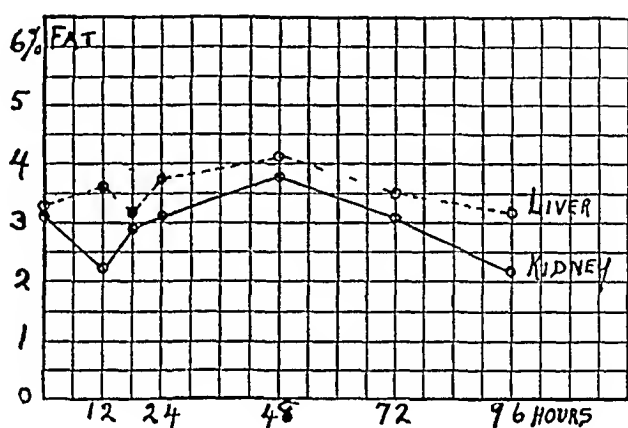


Chart 4—The percentage of lipid in the kidney and liver at different intervals, following the onset of an exacerbation of nephritis in kidneys already the seat of a chronic nephritis

by repeated uranium intoxications. As a result of this nephritis the functional response was lessened. The final injection of uranium did not further materially decrease the function for the reason that an animal develops a tolerance toward the poisoning. Likewise, there was no acidosis as determined by the carbon dioxide of the blood serum. The curves plotting the amounts of extractable lipid varied from those previously obtained. There was not such a marked variation in the amount of lipid, the maximum amount was reached a little later (forty-eight hours), and the decrease at the seventy-two hour period was less. In short, in this group of animals in which a subacute nephritis had been established, a final intoxication not sufficiently large to materially increase the degree of nephritis, failed to materially disturb the lipid content of both kidney and liver. The variation of the lipid content again maintained a definite relation to the functional response.

The increase of stainable lipid material at the six hour period was in a majority of instances more pronounced in the liver. By the extraction method there was a greater increase in the amount of lipid in the

liver, as compared with the kidney, in three of the four series of experiments. The functional response of the liver, could it have been determined as satisfactorily as the response of the kidney, would presumably have shown a diminution.

#### SUMMARY

Our study is concerned with the question of a possible relationship between the amount of lipid material in the kidney in acute nephritis and its ability to function.

We have estimated the total amount of lipid material in the kidney and in the liver by two methods: (1) by the use of Heixheimer's fat staining technic, (2) by chemical extraction in a Soxhlet apparatus.

In a group of normal animals, the average lipid content of the kidney was 3.43 per cent and of the liver 3.42 per cent.

The kidneys of these control animals did not contain stainable lipid material. The livers contained fine dustlike particles of lipid in the cells in the periphery of the lobules.

An acute nephritis was established in four groups of animals by the subcutaneous injection of uranium nitrate.

The functional response of the kidney in each of these animals was evaluated by a chemical and microscopic examination of the urine, a phthalein determination and readings of the nonprotein nitrogen, urea nitrogen and carbon dioxide of the blood. The amount of stainable and extractable lipid material in the kidney and liver was determined at stated periods from the time of onset of the nephritis.

In these groups, an increase in the amount of extractable lipid preceded any alteration in the functional response of the kidney. A maximum increase of lipid occurred within twenty-four hours, and was followed by a decrease which persisted for as long as fifteen days.

One group of animals was given protective doses of sodium carbonate at the time of injection with uranium nitrate. The decrease in the functional response of the kidney was delayed, but the protective action of the carbonate solution was not sufficient to prevent lipid changes in the kidney and liver or to prevent a marked decrease in the kidney function during the latter days of the experiments.

In a fourth group of animals in which a well developed subacute nephritis was established by weekly injections of uranium nitrate, the functional response of the kidney was little altered by a final intoxication with the metal, and the amount of extractable lipid material was likewise little altered.

#### CONCLUSIONS

An alteration in the amount of stainable and extractable lipid material in the kidney precedes any alteration in the functional response of this organ in acute experimental nephritis.

From our data, a definite relation was found to exist between the lipoid changes in the kidney and the ability of this organ to function. This relationship continued under a variety of experimental conditions.

A close relationship exists between the degree of fatty change in the kidney and in the liver in experimental nephritis.

The amount of extractable lipoid material in the liver is somewhat greater than that in the kidney under the conditions of our experiments, but curves of these changes are comparable.

Chemical extraction of lipoid material is a more accurate method of determining lipoid changes than the microscopic study of stained sections.

Microscopic evidence of the toxic effect of uranium nitrate occurs in the liver earlier than in the kidney.

In the instances in which lipoid changes were lessened or inhibited the ability of the kidney to function was less disturbed.

# HEMOGLOBIN CONTENT OF THE RED BLOOD CELLS IN RELATION TO THEIR SURFACE AREA \*

PRELIMINARY REPORT

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AND

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Hemoglobin estimations have for years been used for diagnostic and prognostic purposes, and have also played a part in the investigation of research problems in both medicine and physiology. Under various clinical and experimental conditions, wide variations in the hemoglobin content of the blood have been noted and numerous suggestions have been made to explain this. They are too numerous even to refer to here. If we take into consideration the phenomena recorded in this communication, it becomes obvious that inferences drawn from the hemoglobin variations are liable to be incorrect.

It is not generally recognized that, under ordinary conditions of life, variations of the hemoglobin content of the blood, even to the extent of 30 per cent, may and do frequently occur in the same person during the same day. That such variations do occur was brought to the attention of one of us (R) some time ago by Dr A H Gordon, attending physician to the Montreal General Hospital. Observations were then being made on the blood of a patient suffering from pernicious anemia. Attention was drawn to the fact that the results of the hemoglobin determination made on this patient one particular afternoon showed a wide discrepancy from that made during the forenoon of the same day. Repeated observations made thereafter on the same person gave very irregular results.

A careful search of the literature proved that records of this phenomenon are very scanty<sup>1</sup>. Because of this, observations were made on a series of twenty apparently normal persons with this special point in view. The routine habits of the individual as to diet, time of meals, etc., were not disturbed. Hemoglobin estimations were made every two hours during the day from 8 00 a m until 6 00 p m. The blood was obtained by venous puncture and the hemoglobin calculated from the oxygen carrying capacity, by means of the formula of Van Slyke. The

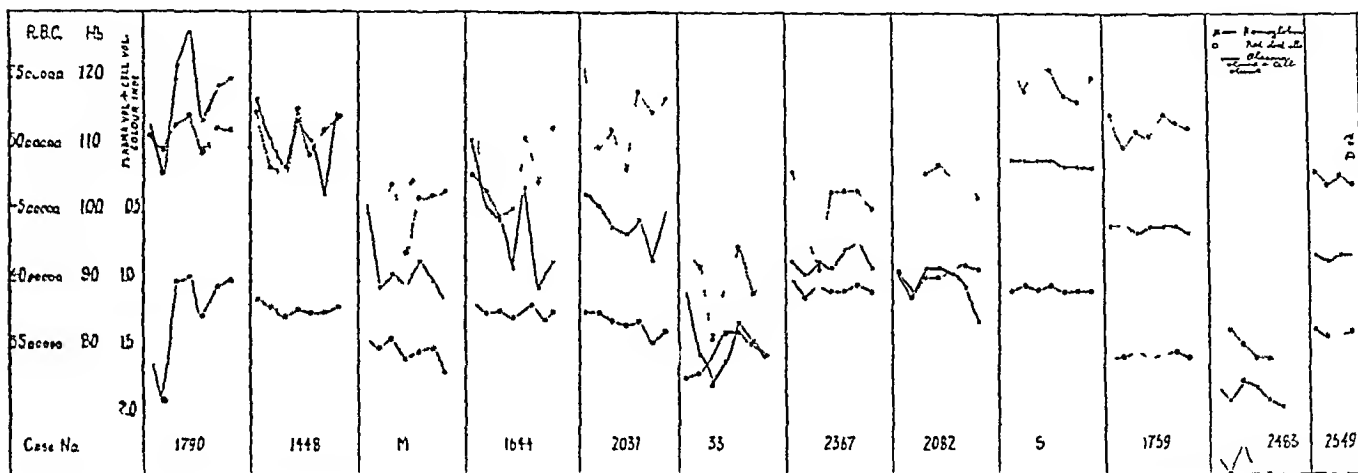
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\*From the Department of Metabolism, Montreal General Hospital

1 Dreyer, G, Bazett, H C, and Pierce, H F. Lancet 2 588 (Sept 18) 1920

results of these observations have already been reported<sup>2</sup> It appears to be an established fact that marked variations, even to the extent of 30 per cent in the hemoglobin content of the blood, may occur in the same person in the same day

Since then, further studies have been made under varying conditions, and an attempt was made to determine the possible factors governing these variations Diets, consisting of constant intake of solids and fluids, and meals given at definite periods of the day failed to alter the variation curves Rest in bed, with the minimum essential muscular movements, and the presence or absence of fever seemed to bear no relation to them One observation which is of interest is that in practically all patients with advanced heart failure, a marked fixation in the hemoglobin curves was noted



Hemoglobin, cell count, blood volume time curve

The principal object of this paper is to record a phenomenon which does not appear to have been hitherto reported That is the relation between the surface area of the red blood cells and their hemoglobin content Following the first twenty observations, which were made on hemoglobin content only, an attempt was made to co-ordinate the hemoglobin data with those of cell counts, color indexes and proportion of plasma to cell volume In Table 1 are found the combined data and these are graphically recorded in the chart For brevity, only type cases are shown representing the different types of curves noted

#### TECHNIC

All cell counts were made by the same person (S), and represent the average of three readings, all varying within 100,000 The hemoglobin determinations were made by the Van Slyke (oxygen carrying



capacity) method. The proportions of plasma and cell volume were obtained by centrifugating all the blood specimens of the same individual, at the same time, in separate glass tubes of equal bore, for thirty minutes at 3,000 revolutions a minute.

## RESULTS

The interpretation of the data in cases number 1790 and number 33 do not appear to present any difficulty. Since the percentage of hemo-

TABLE 1—*The Combined Data of Hemoglobin and Cell Counts*

Time	Red Blood					Red Blood					Red Blood			
	Cells	Hb	P/C*	I**		Cells	Hb	P/C	I		Cells	Hb	P/C	I
8 a m	5 10	114	1 37	1 11		5 29	117	1 14	1 10		5 19	102	1 42	0 93
10 a m	4 96	106	1 88	1 07		4 85	111	1 18	1 14		4 51	89	1 50	0 98
12 m	5 17	122	1 00	1 18		4 79	106	1 25	1 10		4 72	91	1 43	0 96
2 p m	5 25	128	0 96	1 22		5 31	114	1 21	1 07		4 21	89	1 57	1 05
4 p m	4 96	114	1 25	1 14		4 97	111	1 23	1 11		4 62	93	1 53	1 00
6 p m	5 15	119	1 04	1 15		5 12	113	1 22	1 10		4 64	90	1 50	0 97
8 p m	5 13	120	1 10	1 16		5 25	116	1 19	1 10		4 68	87	1 66	0 92
1790						1448					M			
8 a m	4 80	111	1 14	1 17		5 61	103	1 23	0 91		4 26	89	1 72	1 04
10 a m	4 69	101	1 24	1 07		5 00	101	1 24	1 01		4 21	79	1 69	0 93
12 m	4 47	99	1 21	1 10		5 13	98	1 30	0 95		3 56	75	1 76	1 05
2 p m	4 54	92	1 26	1 01		4 74	97	1 33	1 02		3 97	78	1 39	0 98
4 p m	5 09	104	1 16	1 02		5 41	99	1 30	0 91		4 29	84	1 36	0 97
6 p m	4 75	89	1 29	0 93		5 28	93	1 47	0 89		3 91	81	1 45	1 03
8 p m	5 15	93	1 23	0 90		5 36	101	1 37	0 94		4 04	78	1 56	0 96
1644						1037					33			
8 a m	4 81	93	0 96	0 96		4 77	91	0 95	0 95		5 65	108	1 06	0 95
10 a m	4 36	91	1 13	1 04		4 08	88	1 10	1 07		5 41	108	1 04	0 99
12 m	4 09	93	1 03	1 13		4 81	92	0 97	0 95		5 64	108	1 06	0 95
2 p m	4 66	92	1 07	0 98		4 88	91	0 97	0 93		5 56	103	1 04	0 97
4 p m	4 69	95	1 06	1 01		4 78	89	0 93	0 93		5 39	107	1 08	0 99
6 p m	4 69	96	1 03	1 02		4 86	87	0 89	0 89		5 48	107	1 08	0 97
8 p m	4 54	92	1 07	1 01		4 62	84	0 91	0 90		5 52	107	1 08	0 97
2367						2082					S			
8 a m	5 25	97	1 57	0 92		3 42	74	2 30	1 08		4 81	94	1 36	0 98
10 a m	5 50	97	1 57	0 88		3 65	72	2 50	0 96		4 72	93	1 41	0 98
12 m	5 12	96	1 54	0 93		3 52	75	2 22	1 06		4 80	94	1 40	0 90
2 p m	5 09	97	1 57	0 95		3 43	74	2 40	1 07		4 75	94	1 39	0 98
4 p m	5 25	97	1 55	0 92		3 41	72	2 60	1 05		Died			
6 p m	5 19	98	1 54	0 94		3 40	71	2 64	1 04					
8 p m	5 15	97	1 57	0 94										
1759						2483					2549			

\* P/C = plasma volume — cell volume

\*\* I = color index

globin varied practically inversely as the proportion of plasma to cell volume, the variations in these cases appear to be a function of the dilution of the blood. This also appears to explain the marked fixation of the curves in the last four cases, number S, number 1759, number 2483 and number 2549. All of these were patients with advanced heart failure. The fixation here may be attributed to the slowing of the circulation of the body fluids. In the remainder of the cases, however, there is one feature noted, common to all, namely in spite of the marked variations, both in the cell count and hemoglobin content, there was a

fixation in the proportion of plasma to cell volume. This appears to be of clinical significance. A tentative explanation of this phenomenon is suggested.

Since two different specimens of blood, of equal volume, present the same proportions of plasma to cell volume, and since one contains more cells per cubic millimeter than the other, it appears reasonable to assume that the cells of the latter must be of small dimensions. Such a phenomenon, variations in the size of the cells, is generally recognized. The possible variations due to the difficulties met with in hematocrit determinations do not explain the wide discrepancies noted. This decrease in the size of the cell does not, however, explain the presence of the variations in the hemoglobin if we accept the prevalent view that the hemoglobin is contained within the cell. It is obvious that the smaller the cells, with a corresponding increase in number for a given volume of fluid, the greater will be the total cell surface. For this reason it is suggested that the hemoglobin is not contained within the

TABLE 2—*The Law of Hemoglobin Distribution*

	Hb Content per 100 C c Blood	Red Blood Cells per Mm. in Millions	Average of Single Cell in Gm 20 by $10^{-12}$ 8 by $10^{-12}$	Surface of One Blood Cell in $\mu^2$ 68.4 25.1	Average Hb Content per $\mu^2$ Surface in $10^{-14}$ Gm 27 29
Rabbit	11.9	5.86			
Goat	10.9	13.94			

cell, but is distributed on the surface. This appears to be the rational explanation of the observations made in the cases recorded. This view, if correct, opens a new problem as to the structure and composition of the red blood cells. Of interest to note here are the recent observations of two independent workers, Burkner,<sup>3</sup> and Brinkman and Szent-Gyorgyi.<sup>4</sup> Burkner demonstrated a law, that the corpuscular amount of hemoglobin is proportional to the cell surface. Taking as an example cells of different size (rabbit and goat) the law "Haemoglobinverteilungsgesetz" is demonstrated (Table 1).

More recently, the series of experiments by Brinkman and Szent-Gyorgyi on the electrical conductivity and refractive indexes of partially and totally hemolyzed blood, further strengthen the view that the hemoglobin is not contained within the cell but is distributed about the surface.

These observations appear to be of clinical interest. If the percentage of hemoglobin is a function of cell surface and is dependent on the

<sup>3</sup> Burkner, K. Arch. f. d. ges. Physiol. **195** 516, 1922, Nature **3** 845 (June 23) 1923, abstr., by E. Gorter.

<sup>4</sup> Brinkman, R., and Szent-Gyorgyi, A. J. Physiol. **58** 204 (Dec.) 1923.

adsorptive capacity of the stroma of the cells, the importance of a wider application of physicochemical methods in the study of the blood in disease is obvious. These observations are not being extended to the various forms of anemia.

# THE EFFECT OF CHOLECYSTECTOMY ON GASTRIC SECRETION \*

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AND

E T McENERY, BS

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It is generally stated that disease of the gallbladder is associated with changes in gastric secretion. Most observers (Holweg,<sup>1</sup> Rohde,<sup>2</sup> Leva<sup>3</sup> and Glaser,<sup>4</sup> and recently Gatewood<sup>5</sup>) have found that hyp acidity and an acidity are present in cases of cholelithiasis and that similar findings are present after cholecystectomy. Other observers,<sup>6</sup> however, have stated that hyperacidity and hypersecretion occur in cases of cholecystitis and in gallbladder disease associated with biliary retention. Thus Simnitsky<sup>7</sup> found hyperacidity in obstruction of the common duct in man and animals.

These observations, particularly the alleged persistence of change in gastric secretion after cholecystectomy, led us to inquire into the relation of the gallbladder to the gastric secretory mechanism. Besides making a study of the effect of cholecystectomy on gastric secretion, we have studied the effect of bile on gastric secretion and have examined the mucosa of the gallbladder for the presence of a gastric secretin.

## PROCEDURE

Pawlow pouches were made on five dogs. Their normal gastric secretory response to a test meal of 250 gm of hamburger was determined by making from ten to twenty control experiments in each dog prior to cholecystectomy. The procedure of each experiment was to collect the continuous secretion for from one to two hours, then feed the test meal and collect the secretion at hourly intervals for from three to five hours. The secretion was titrated for free and total acidity and the pepsin content was determined by Mette's method. After adequate controls, the gallbladder was removed and the secretory response to

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\*From the Hull Physiological Laboratory of the University of Chicago.

1 Holweg. *Deutsch Arch f klin Med* **108** 255, 1912.

2 Rohde, C. *Arch f klin Chir* **115** 727 (March) 1921.

3 Leva. *Arch f Anat* **132** 490, 1893.

4 Glaser. *Wien Med Wchnschr* **55** 1430, 1905.

5 Gatewood. *Achlorhydria in Gallbladder Disease*, J. A. M. A. **81** 904 (Sept 15) 1923.

6 Griffiths, H. E. *Lancet* **1** 265 (Feb 10) 1923.

7 Simnitsky. *Berl klin Wchnschr* **38** 1077, 1901.

the test meal was followed daily for seven days, and then at intervals of from three to five days for periods of from three weeks to three months

The animals were dressed daily, and carefully fed and cared for so as to prevent any of the several factors that cause a depression of gastric secretion from entering

In our experiments on the effect of bile on gastric secretion, we gave from 25 to 50 c c of bile obtained from the gallbladders of normal dogs to dogs prepared by the Pawlow pouch method by stomach tube and observed its effect on the secretion of the pouch

We also applied bile to the intestinal mucosa of a dog prepared with a Thiry's fistula of the jejunum and a gastrostomy, in order to ascertain the effect of bile on the gastric secretion when in the intestine

In order to ascertain whether or not a gastric secretion was present in the gallbladder mucosa, we obtained 350 gm of freshly killed hogs' gallbladder and extracted it according to the method of Keeton and Koch,<sup>8</sup> and so diluted the extract that 1 c c was equivalent to the amount of 10 gm of gallbladder. This was injected subcutaneously into the dogs prepared by the Pawlow pouch method in 3 c c doses, to test for the presence of a gastric secretion

#### RESULTS

Dogs 1 and 2 were studied for twenty-five and twenty-six days, respectively, following cholecystectomy. Dogs 3 and 4 were studied for eighty-seven and 113 days, respectively, after cholecystectomy. Dog 5 died of multiple liver abscesses on the seventh day after cholecystectomy. This animal showed an achylia during the seven day period.

Our results on the four dogs are shown in a condensed form in Tables 1 and 2. It will be seen from these tables that three of the four dogs showed either an achylia or a hyposecretion for from three to eight days after cholecystectomy, the other dog secreting normally on the second day after. None of the animals showed an achylia or even a hyposecretion after the immediate effects of the operation had disappeared. On the contrary, they secreted normally (Dog 3) or greater than normally (Dogs 1, 2 and 4). This hypersecretion is especially evident in Dog 4. It first appeared and was very evident on the day that the animal first ate normally, following the postoperative hyposecretion or achylia, which was associated with anorexia.

Necropsy on Dogs 1, 2, 3 and 4 showed the common bile duct to be slightly dilated, measuring 6 mm, 5 mm, 6 mm and 6 mm, respectively, in diameter when collapsed. Fibrous adhesions were present at the site of operation in Dog 2, but the other dogs were free from adhesions.

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<sup>8</sup> Keeton & Koch. *Am J Physiol* 37 481, 1915

We have also observed that two of these cholecystectomized dogs respond normally to gastrin, histamin and other known gastric excitants

Bile, when given in 50 c c amounts by stomach tube to dogs prepared by the Pawlow pouch method, definitely stimulates gastric secretion. This is especially true if the glands are in tone, i e., secreting free acid, at the time the bile is given (Table 3)

Our results on the application of bile to the intestine (Table 3) show that the stimulating action of bile comes chiefly, if not entirely, from its action in the intestine

TABLE 1—*Effect of Cholecystectomy on Gastric Secretion on Dogs Prepared by Pawlow Pouch Method*

Procedure	Amount of Secretion in Cc			Free Acidity			Total Acidity			Average Pepsin in Mm
	Mini-mum	Maxi-mum	Average	Mini-mum	Maxi-mum	Average	Mini-mum	Maxi-mum	Average	
Dog 1										
Before cholecystectomy	7	55	20	25	110	67	40	104	75	80
3 days after			3			17			25	80
7 days after			25			87			100	80
Next 3 weeks after	24	35	30	70	110	88	87	126	105	80
Dog 2*										
Before cholecystectomy	6	21	12	33	57	45	52	80	67	80
1st 3 days after		achylia								
4 days after			4			22			35	
8 days after			24			99			108	80
Next 3 weeks	5	42	18	20	112	50	50	120	67	42

\* Adhesions found at necropsy. Data presented are the secretions collected for three hours after a test meal

TABLE 2—*The Effect of Cholecystectomy on Gastric Secretion on Dogs Prepared by the Pawlow Pouch Method*

Procedure	Amount of Secretion in Cc			Free Acidity			Total Acidity			Average Pepsin in Mm
	Mini-mum	Maxi-mum	Average	Mini-mum	Maxi-mum	Average	Mini-mum	Maxi-mum	Average	
Dog 3										
Before cholecystectomy	18	37	26	44	100	74	57	115	90	60
On 2 days after			15			55			80	80
Next 85 days	16	49	28	27	100	60	40	110	80	50
Dog 4										
Before cholecystectomy	6	22	12	10	65	35	33	82	60	90
1st 8 days after		achylia with poor appetite								
9th day after			51			100			115	60
Next 14 days	5	16	8	10	60	40	30	80	62	
Next 17 days	32	48	42	55	110	85	75	137	115	80

Our results (Table 3) on the presence of a gastric secretin in the gallbladder show unquestionably that such a secretin is present, and approximately to the same degree that it is present in the pyloric mucosa

In connection with our experimental studies, we are able to report the preoperative and postoperative gastric findings in gallbladder disease treated by cholecystectomy. The cases reported are from the service of Dr. Friend, Michael Reese Hospital, and the diagnoses were confirmed by the pathologic report. In reviewing eighty cases of cholecystectomy, we were only able to find five cases in which a gastric analysis

had been done after cholecystectomy The results are presented briefly in Table 4 In two of the five cases, cholecystectomy caused no change (Cases 4 and 5) in gastric secretion, whereas in two (Cases 1 and 2) there was a reduction in acidity In Case 3 no preoperative gastric analysis was made, but, at any rate, the cholecystectomy certainly did not cause either subacidity or an achylia as some claim

TABLE 3—*Effect of Bile on Gastric Secretion and the Presence of a Gastric Secretion in the Gallbladder on Dogs Prepared by the Pawlow Pouch Method*

Procedure	Time o'Clock	Gastric Secretion			
		Amount, Cc	Free Acidity	Total Acidity	
Continuous secretion 50" bile by stomach tube	11-12	6.5	22	35	
	12-1	5.7	25	50	
	1-2	11.0	50	80	
	2-3	10.3	67	90	
	3-4	9.0	50	70	
	4-5	7.5	45	72	
Continuous secretion 50" bile by stomach tube	12-1	0.7	42	67	
	1-2	1.3	62	80	
	2-3	4.6	90	102	
	3-4	2.2	100	110	
	4-5	1.2	80	92	
	5-6	1.2	80	95	
Continuous secretion Bile applied to intestine*	1-3	1.5	0	17	Latent period 15 min
	3-3.45	22.0	72	105	
	3.45-4.00	10.0	72	105	
	4.00-4.30	1.2	50	75	
Continuous secretion 3" gastrin from gallbladder	3-4	3.1	0	12	Subcutaneously
	4-5	23.5	92	110	
	5-6	26.0	130	137	

\* Dog prepared with a Thury's fistula of the jejunum and a gastrotomy

TABLE 4—*The Effect of Cholecystectomy on Gastric Secretion in Five Cases of Cholecystitis in Man*

Case	Diagnosis	Preoperative Gastric Analysis			Date of Operation	Postoperative Gastric Analysis			Remarks
		Date	Maximum Free Acid	Maximum Total Acid		Time Since Operation	Maximum Free Acid	Maximum Total Acid	
1	Chronic cholecystitis	4/20/23	20	32	4/26/23	17 d	7	10	Subacidity
2	Chronic cholecystitis	3/ 1/19	30	76	4/28/22	17 mo	23	27	Subacidity
3	Chronic cholecystitis					2 mo	62	72	Same as Case 2 before operation
4	Chronic cholecystitis	5/23/22	35	45	5/27/22	22 d	35	43	No change
5	Cholelithiasis	5/16/21	15	25	5/30/21	2 yr	17	25	No change

Lactate ten meals with fractional analysis

COMMENT

Our experimental results show that cholecystectomy in dogs prepared by the Pawlow pouch method does not result in permanent hyposecretion or achylia, which may be present, however, for a short period

after the operation, due, we believe, to the direct effect of the operation and not to the absence of the gallbladder per se. On the other hand, a variable hypersecretion may be observed in some animals. The immediate hypersecretion that occurred in Dog 4 on the ninth day after operation is probably a starvation effect, as it has been observed by Kunde that hypersecretion of gastric juice frequently occurs in dogs prepared by the Pawlow pouch method, following a short or prolonged period of starvation, an observation that has been frequently observed by one of us (Ivy) in the course of other studies on gastric secretion. It is difficult to explain the continued hypersecretion that we have observed following cholecystectomy. We believe that the explanation involves the solution of two questions: (1) Does the normal gallbladder reflexly inhibit gastric secretion? and (2) how does cholecystectomy influence the discharge of bile into the intestine? We cannot answer these two questions by direct evidence. We do not doubt, however, that some reflex inhibitory mechanism is present, which best accounts for the large percentage of achlorhydrias and hypo-acidities seen in gallstone disease, but it is difficult for us to believe that such an inhibitory mechanism is functioning in the case of the normal gallbladder as it occurred in the dogs used in our experiments.

It is commonly assumed that the removal of the gallbladder causes a more continuous flow of bile into the intestine. This assumption is questioned by Rost,<sup>9</sup> who reports that bile is not always discharged continuously following cholecystectomy. Nevertheless, the explanation of the hypersecretion, when it occurs, is related to the rôle that the bile plays in the digestion of fats and in the causation of the secondary phase of gastric secretion. Our results show that bile itself stimulates gastric secretion, which confirms Sokolov's<sup>10</sup> observations. It has been shown that soaps, fatty acids and glycerol, which are products resulting from the cleavage of fats, stimulate gastric secretion when introduced into the intestine.<sup>11</sup> It is well known that fats inhibit gastric secretion. Thus, it is evident that if bile is made more available by removal of the gallbladder, or any other procedure, gastric secretion will be augmented.

Our results agree in part, but not entirely, with the observations of other experimenters on animals. Holweg<sup>1</sup> observed a diminished acidity, and anacidity, in three out of four dogs, following cholecystectomy. Rohde<sup>2</sup> made similar observations. Dangschat<sup>12</sup> reported that two out of eight dogs showed diminished acidity following cholecystectomy. Rost<sup>9</sup> observed similar results on eleven dogs. Recently Gate-

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9 Rost. *Mitt a d Grenzgeb d Med u Chir* **26** 710, 1913

10 Sokolov. Quoted by Pawlow. *The Work of the Digestive Glands*, London, C Griffin and Co, 1910

11 Ivy, A. C., and McIlhain, G. V. *Am J Physiol* **67** 124 (Dec.) 1923

12 Dangschat. *Beit z klin Chir* **128** 605, 1923



wood<sup>5</sup> reported no change in acidity and secretion in two dogs after cholecystectomy. Since none of these investigators used the Pawlow pouch method on dogs, the ideal preparation for the study of gastric secretion, we are inclined to question the value and accuracy of their observations.

Investigators who have observed a decrease in gastric secretion following cholecystectomy have offered the following explanations: (1) On removal of the gallbladder the flow of bile into the intestine is continuous, as no interdigestive storage of bile in the gallbladder can occur. This continuous presence of bile in the intestine inhibits an alleged "intestinal hormone" from exercising its normal stimulating effect on gastric secretion, (2) Simnitsky<sup>7</sup> reported that hyperacidity and hypersecretion occur in animals after ligation of the common bile duct and in icterus, which he believed was due to an assumed inhibitory action of bile in the intestine on gastric secretion. Rost<sup>9</sup> believed that the hypoacidity was due to a diminished secretion of bile and pancreatic juice. In the light of our observations the first two explanations are false, because bile does not inhibit, but excites gastric secretion. Rost's observation lacks confirmation, and we feel that it should be confirmed, because we cannot understand why cholecystectomy should result in a depression of biliary and pancreatic secretion.

The fact that a gastric secretin is present in the gallbladder just adds one more tissue to the already large list of tissues that contain a gastric secretin. We do not believe the presence of a secretin in the gallbladder has any physiologic significance in light of the observations of Keeton, Luckhardt and Koch,<sup>13</sup> of Ivy and Whitlow,<sup>14</sup> and of Lim.<sup>15</sup> If it did play a rôle, we should have observed a depression of gastric secretion in our dogs prepared by the Pawlow pouch method.

The fact that cholecystectomized dogs respond normally to gastrin, histamin, beta-alanine and other excitants shows definitely that their gastric secretory mechanism is fundamentally intact.

Our series of five cases of cholecystectomy adds to the evidence previously presented by Dangschat<sup>12</sup> and Gatewood<sup>5</sup> that achlorhydria does not follow cholecystectomy as maintained by Rydgaard,<sup>16</sup> and that in the majority of patients it remains unaltered.

We feel that clinical reports in many instances fail to take into consideration normal variations in gastric secretion in man. There being many causes for anacidity and achylia, and the clinician not having a record of the normal secretion prior to the disease of the

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13 Keeton, R. W., Luckhardt, A. B. and Koch, F. C. *Am J Physiol* **50** 527 (April) 1920, *Ibid* **51** 454 (April) 1920.

14 Ivy, A. C., and Whitlow, J. E. *Am J Physiol* **60** 578 (May) 1922.

15 Lim. *Quart J Exper Physiol* **13** 79, 1922.

16 Rydgaard, F. *Arch f klin Chir* **115** 511 (March) 1921.

gallbladder, are facts that invalidate conclusions drawn concerning the relation of the gallbladder to the gastric secretory mechanism. A depression of gastric secretion accompanied by cholelithiasis and cholecystitis, or removal of the gallbladder, need not necessarily be related to the failure of function or absence of the gallbladder, but may be due to numerous causes. Gallbladder infection, as is well known, is not limited to the gallbladder, but affects the biliary passages, liver, pancreas and adjoining viscera. Inflammatory reactions and the psychic condition of the patient may account for alteration in gastric curves and analyses. Nutritional, appetite and reflex causes may also be important factors. Alder and Ohly<sup>17</sup> believe that anacidity is a primary disease, and that gallbladder disease is secondary to gastritis. Recently McCarthy<sup>18</sup> has expressed a similar opinion. It is well known that removal of the gallbladder does not prevent subsequent disease of the biliary passages.

Many symptoms, such as pyrosis, diarrhea and constipation, following cholecystectomy have been ascribed to the subsequent achylia. This has led many surgeons to hesitate to perform cholecystectomy and to resort to cholecystotomy. Our observations, however, would lead us to the view that the removal of the gallbladder, per se, is not the cause of the achylia or anacidity when it occurs. The persistence of certain symptoms and clinical findings after cholecystectomy may be due to infection or a disturbance of other associated tissues, such as liver, duodenum and pancreas.

#### SUMMARY

Cholecystectomy in dogs prepared by the Pawlow pouch method does not cause a depression of gastric secretion. In three out of four dogs a variable degree of hypersecretion resulted. Bile in 50 cc amounts stimulates gastric secretion when given by stomach tube or applied to the intestinal mucosa. It is pointed out that bile, through its rôle in the digestion of fats, may have an indirect excitatory action on the gastric secretory mechanism.

A gastric secretin is present in gallbladder tissue, but it is believed to be of no physiologic significance. Changes in gastric secretion associated with gallbladder disease is not due to the breaking down of some hypothetic relation between the gallbladder and the gastric secretory mechanism.

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17 Alder and Ohly. Quoted by Schultz, E. *Arch f Verdauung* **30** 237, 1922.

18 McCarthy, W. C., Alvarez, et al. *abstr., J. A. M. A.* **81** 979 (Sept. 22) 1923.

## Book Reviews

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LABORATORY DIAGNOSIS OF SYPHILIS By HIDEYO NOGUCHI Price \$7 50 Pp 392, with 59 illustrations New York Paul B Hoeber, 1923

Noguchi has presented in this text complete directions for making the important laboratory tests concerned with the diagnosis of syphilis. The first chapters contain detailed discussion of serum hemolysis, and the quantitative relations to be observed with such hemolysis. These facts are presented for the purpose of showing the importance of quantitative procedures in making serum diagnosis of syphilis. Instructions are given for preparing amboceptor and antigens, and for obtaining complement. Noguchi's system of serum diagnosis is described in detail, also Wassermann's technic. A discussion of the value of the serum diagnosis of syphilis is contained in one chapter. Another is concerned with the effect of treatment on this test. Mention is made of the luetin reaction, and its significance in tertiary, and congenital syphilis. A chapter considers examinations of the spinal fluid. In this are mentioned globulin tests and the procedure and significance of the Lange colloidal gold reaction. In the last portion of the text are given instructions for the dark field examination, the morphologic similarities and differences between *Spirochaeta pallida* and other spirochetes, as well as special staining methods for demonstrating spirochetes in slide and fixed tissue preparations.

The text is recommended to those finding this detailed technic a part of their routine work. The clinician will find helpful the chapters dealing with the significance of, and the effect of treatment on, the serum diagnosis in syphilis.

METHODIK DER RONTGENTIEFENTHERAPIE By DR ERNEST POHLE and HANS JARRE, Dresden Theodor Steinkopff, 1923

A creditable exposition is made of the basic principles of roentgen-ray absorption necessary for the treatment of deep lying malignancy by short wave rays. Filtration tables and absorption diagrams after the general plan of Dessauer are given. Individual chapters are devoted to the physical principles underlying the treatment of carcinoma of the breast, rectum and uterus. Two short chapters deal with the castration dose and with carcinoma of the larynx.

ZUR THERAPIE DES KARZINOMS MIT RONTGENSTRAHLEN By F DESSAUER Paper cover Price, 40 cents, second edition (monograph) Dresden and Leipzig Theodor Steinkopff, 1923

This monograph is the printed form of four lectures. The first discusses the treatment of carcinoma with physical methods, and the possibility of thereby attaining the desired results, the second deals with the electrotechnical basis of deep roentgen-ray therapy, the third with the dispersion and distribution of roentgen rays in the material, and the fourth with the practical application of the physical portion to deep therapy. The monograph is chiefly theoretical, contains very little new or especially instructive and makes no mention of clinical results.

There are two other related monographs in this series, both on a par with the one reviewed in detail.

## THE MECHANISM OF ANGINA PECTORIS

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Although the clinical syndrome, known as angina pectoris, has been carefully studied by many observers it seems fair to assert that the exact condition of the heart or the sequence of events occurring during an anginal attack is unknown. It is true that theories have been promulgated, but their very multiplicity is good evidence that there is no general agreement in the profession as to the cause of angina pectoris. It is my purpose in this paper to offer a conception of angina pectoris which seems, may I say, to contain a more satisfactory explanation of this dread condition. I hasten to deny that I hold as original all aspects of the theory to be presented below.

### DEFINITION

It is well at this point to pause to define what is meant by the term angina pectoris. Typical angina pectoris is characterized<sup>1</sup> by paroxysmal attacks of pain over the sternum, often radiating to the left shoulder and arm, and commonly associated with a sense of impending death. The attacks usually follow closely on exertion, physical or mental. Considerable variation exists in the intensity of the symptoms, many cases are observed in which the symptoms are not well developed or are atypical in their character. With cessation of all exertion the attack comes to an end, the quick acting vasodilators commonly bring relief. Sudden death is prone to occur.

### THE LEADING THEORIES

It is necessary, for the purpose of this paper, to refer to but three of the leading theories of the cause of angina pectoris.

1 *Coronary*—(a) Sclerosis of the coronary arteries. In 1799, Parry and Jenner<sup>2</sup> first interpreted the clinical syndrome known as angina pectoris as due to calcification of the coronary arteries. However, sclerosis of the coronary arteries is frequently found on post-

1 Reid, W D. The Heart in Modern Practice, Philadelphia, J B Lippincott Company, 1923, p 187.

2 Parry and Jenner. An Inquiry Into the Symptoms of the Syncope Anginosa, Commonly Called Angina Pectoris, London, 1799, quoted by Gross, L. The Blood Supply of the Heart, New York, Paul B Hoeber, 1921, p 79.

mortem examination of cases in which angina pectoris had not occurred, and angina pectoris may occur in patients whose coronaries are proved to be free of sclerosis. The explanation of coronary sclerosis has, therefore, been largely abandoned.

(b) Claudication of the coronary arteries. Claudication, or spasm of the artery, causing a deficiency of the blood supply of the myocardium is assumed to take place, an analogy to intermittent claudication in the leg is pointed out. This theory is the one generally held by those who believe the cause of angina pectoris is to be found in the coronary arteries, and who appreciate that to attribute angina pectoris to sclerosis of the coronaries is, in the present state of medical knowledge, untenable.

At first the theory is plausible, and has received wide acceptance. I have been unable, however, to find any real proof of the existence of the phenomenon of claudication in the arteries of the heart in spite of an extensive search of the literature and the guidance of some well qualified observers who believe in this theory.

In 1909, Wiggers (Am J Physiol 24 391 [July 1] 1909) stated that the coronary arteries are supplied with vasomotor nerves. It has been demonstrated (J Physiol 42 132 [March 28] 1911) that epinephrin, though it exerts a constrictor effect on most peripheral arteries, causes a dilatation of the coronaries. My study of the literature of experimental physiology leads to the belief that the coronary arteries are mostly passive as regards their caliber, and whatever vasomotor influence they experience is dilator in effect. Since writing the foregoing, I find that Prof W M Bayliss in his monograph (The Vaso-Motor System, New York, Longmans, Green & Co, 1923, pp 28 and 62) expresses a similar opinion. (For an adequate presentation of the arguments against the coronary theories of angina pectoris, the reader is referred to the mass of data marshaled by Sir Clifford Allbutt<sup>3</sup> in his book *Diseases of the Arteries, Including Angina Pectoris*.)

2 *Aortic*—Allbutt has written<sup>3</sup> very compellingly in favor of this theory. In brief, angina pectoris is held to be due to irritation of the nerve end plates in the first part of the aorta by the plaques of an aortitis, and is especially liable to occur in conditions causing a rise of the intra-arterial pressure and subsequent stretching of the investing membranes of the root of the aorta. There may be a partial analogy to the pain, caused by dragging on the mesentery. The theory has gained many adherents, among whom may be numbered that authority on the heart, Prof K F Wenkebach of Vienna.

In my opinion, however, Allbutt gives too little place to the concomitant involvement of the myocardium by the *Spirochaeta pallida* as

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3 Allbutt, Clifford. New York, The Macmillan Company, 1915, *Diagnosis and Treatment of Angina Pectoris*, Lancet 1 883 (May 5) 1923.

well as the aortic wall in syphilis, and also I find that one of the chief authorities <sup>4</sup> he quotes as having shown that there were nerve end plates in the first part of the aorta also found them in the heart itself <sup>5</sup>

3 *Myocardial fatigue*—Mackenzie <sup>6</sup> frankly states that he is not sure of the cause of angina pectoris, but considers it some sort of heart exhaustion and treats on that basis

#### THE SOLUTION OF THE PROBLEM NOT IN PATHOLOGY

Angina pectoris is a functional condition just as are the various arrhythmias, and heart failure of the congestive type. It is most commonly associated with three of the types of heart disease, namely, arteriosclerotic heart disease, cardiovascular syphilis (and occasionally in other infections of the heart), and hypertensive heart disease. When the pathologist examines the heart he finds the changes that occur in the respective heart disease with which the anginal syndrome was associated. It has proved no more possible to pick out just what lesion is associated with angina pectoris than it is to determine, on the necropsy table, the cause of premature beats which may have been noted by the clinician.

Just as the nature of other functional conditions of the heart has been disclosed by studies on living animals and man, so, it is suggested, should be sought the solution of the enigma of angina pectoris. Pathology cannot unravel the problem of angina pectoris, let us see if physiology, both normal and pathologic, will not serve better.

#### THE PHYSIOLOGY OF EXERCISE

Typical angina pectoris is characterized by a close connection with exercise, physical or mental. When seized by an attack of angina, the victim practically always remains motionless and cessation of activity often brings him relief.

In attempting to put on paper a statement of the circulatory changes which take place in exercise one is on somewhat uncertain ground as, in spite of extensive studies, the physiologists are not in agreement as to the circulatory phenomena associated with exertion. Therefore, we as clinicians must tread circumspectly but yet with courage, as along this pathway, it would appear, lies the understanding of angina pectoris.

We are indebted to the late F. A. Bainbridge <sup>7</sup> for the following description. "The constriction of the splanchnic vessels, which occurs at the very outset of exercise, raises the pressure at which it is sent

4 Dogiel, A. S. Die sensiblen Nervenendigungen im Herzen und in den Blutgefassen der Säugethiere, Arch f. micr. Anat. **52** 44, 1898.

5 No disparagement is intended by this statement.

6 Mackenzie, J. Oxford Med. **2** 387, 1920.

7 Bainbridge, F. A. The Physiology of Muscular Exercise, New York, Longmans, Green & Company, 1919, p. 49.

into their blood vessels. The greater flow of blood into the active muscles, thus brought about, allows them at once to send more blood into the great veins, and thence to the heart. But the output of the heart does not increase during exercise, as Kioh<sup>8</sup> has shown, until time has elapsed for this to take place. Hence the machinery, by which the output of the heart increases during exercise, is set in motion by the purely mechanical action of the active muscles, and in this manner the blood flow to the muscles, at least so far as this depends on the output of the heart, is very largely determined by their own activity. Dilatation of the blood vessels in the muscles, so far as it occurs during exercise, will allow still more blood to enter these vessels in a given time, and will thereby enhance the return of blood to the heart."

Hooker's<sup>8</sup> picture of the events is somewhat as follows. At the outset there is a local vascular dilatation in the active muscles, coincident with an expression of blood from the veins. This results in a prompt rise of the venous pressure. The consequent transitory fall of the arterial pressure level, or an elevation of the temperature of the venous blood, is followed by an accelerated heart rate. Finally a compensatory vasoconstriction takes place in the great splanchnic area, including the portal vein which shunts the blood to the active muscles. There is, as a consequence, a venous plethora which expresses itself as a rise of venous pressure which continues throughout the period of activity.

The pressure in the peripheral arteries undergoes changes. It seems generally agreed that in normal individuals a rise in the systolic blood pressure<sup>9</sup> is a constant feature of exercise. The diastolic pressure, however, has not received equal attention. In his recently published studies of blood pressure and pulse rate reactions Addis<sup>10</sup> found that the diastolic pressure level fell during exercise, while excitement caused a slight rise. The diastolic pressure is, moreover, distinctly more stable than is the systolic level.

Discussion of the changes in the size of the heart during exercise, and the question of whether the increase of its output per minute is

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8 Hooker, D. R. Effect of Exercise Upon the Venous Blood Pressure, *Am J Physiol* **28** 235, 1911.

9 Bowen, W. P. Changes in Heart-Rate, Blood-Pressure, and Duration of Systole Resulting from Bicycling, *Am J Physiol* **2** 59, 1904. Lowsley, O. S. The Effect of Various Forms of Exercise on Systolic, Diastolic and Pulse Pressures and Pulse Rate, *ibid* **27** 446, 1911. Dawson, P. M. Effect of Training on Blood Pressure in Man, *ibid* **50** 443, 1919. Dedichen, L. Influence of Physical Effort on the Heart, *Acta Med Scandinav* **53** 738 (Jan 14) 1921, abstr, *J A M A* **76** 903 (March 26) 1921. Barringer, T. B., Jr. Principles Underlying the Treatment of Heart Disease by Exercises, *J A M A* **77** 7 (July 2) 1921.

10 Addis, T. Blood Pressure and Pulse Rate Levels, First Paper, *Arch Int Med* **29** 539 (April) 1922, Blood Pressure and Pulse Rate Reactions, Second Paper, *ibid* **30** 240 (Aug) 1922.

achieved by an increase of the heart or output per beat, or both, will be waived as not being essential to the purposes of this paper

The participation of the nervous system is surely a part of the physiology of exercise. Starling<sup>11</sup> writes, "In the quickening of the heart, which accompanies bodily exercise, another reflex mechanism comes into play, to which attention has been called by Bainbridge. Any distention of the right auricle evokes a reflex quickening of the pulse rate, chiefly by diminishing the vagus tone but also probably to a less extent by reflex stimulation of the reflex accelerator nerves. It thus seems that the heart is connected with the heart center in the medulla, governing its rate of beat, by two sets of afferent nerves, which are stimulated by a rise of pressure within the cavities to which they are distributed. Stimulation of one set coming from the arterial end, e. g., the left ventricle, causes a reflex slowing of the heart. Stimulation of the other set which are distributed to the venous end of the heart, evokes increased frequency of the heart beat. Both these sets of impulses are of great importance in correlating the activity of the heart and the amplitude of the circulation with the metabolic needs of the body as a whole."

#### THE DEPRESSOR NERVE

Certain phenomena, occurring in the peripheral circulation during exercise more especially the lowering of the diastolic pressure observed by Addis,<sup>10</sup> appear to be associated with the action of the depressor nerve. This nerve receives scant attention in the anatomic textbooks. In certain of the lower animals, i. e., the rabbit and the cat, the depressor nerve runs as a separate cord but in man it is represented simply by some fibers of the vagus trunk. Dogiel,<sup>4</sup> before mentioned, found its endings in the first part of the aorta and in the endocardium and pericardium, especially of the auricle. Smirnow,<sup>12</sup> whose work antedated that of Dogiel, reported that the end plates of sensory nerves are found in the whole thickness of the endocardium of the auricles and their sheaths, less frequently in the ventricular endocardium and in the connective tissue of the myocardium.

If this nerve is divided there is, according to one<sup>13</sup> of the earliest studies of its function normally no change in the action of the heart or blood pressure, and the same holds true if its peripheral end is stimulated. If, on the other hand, its central cut end be stimulated, a marked fall in blood pressure and slowing of the heart follow. The former is

11 Starling, E. H. *Principles of Human Physiology*, Ed. 3, Philadelphia, Lea & Febiger, 1920, p. 1024.

12 Smirnow, A. *Ueber die sensiblen Nervenendigungen im Herzen bei Amphibien und Säugethiere*, Anat. Anz. **10** 737 (July 10) 1895.

13 Ludwig and Cyon. *Ber. d. sächsischen Gesellsch. d. Wiss., math. phys. Cl.* p. 319, 1866, quoted by Janeway, T. C. *The Clinical Study of Blood-Pressure*, New York, D. Appleton and Company, 1907, p. 14.



held to be due to an inhibition of the vasomotor center, the latter, since it never occurs after division of the vagi, must be dependent on stimulation of the center for those nerves. Hunt<sup>14</sup> writes that the dilatation caused by stimulation of the depressor nerve is of greater extent in the splanchnic area than in the muscular system.

Burton-Opitz<sup>15</sup> considers the depressor nerve plays an important part in varying the resistance in the vascular channels against which the heart must act. In his opinion, this reflex lessening of the peripheral resistance places the cardiac muscle in a much more favorable position to contract without strain.

Since knowledge of the depressor nerve does not appear to be widespread, it may be helpful to refer briefly to a few other papers which deal with or mention the action of this nerve. Koster and Tschermak<sup>16</sup> believe that the depressor reflex has its origin mostly from the arch of the aorta. Martin and Stiles<sup>17</sup> hold that the actual working of the depressor nerve is not limited to the inhibition of existing vasoconstrictor tone. There is an enlisting of vasodilators in the response, and a certain share of the loss of pressure is to be referred to this action.

Stewart,<sup>18</sup> in his remarkable work on experimentally produced insufficiency of the aortic valve, obtained evidence of the operation of the depressor nerve. In fact, he believes that the collapsing type of pulse is not due to regurgitation of blood but to a backward pressure which in turn excites the depressor nerve reflex. Stewart's work, I am aware, has not obtained general acceptance but it may be pointed out that the results of Zollinger's<sup>19</sup> experiments are largely in agreement. MacCallum<sup>20</sup> has presented experimental data which are not in accord with those of Stewart but, since he employed an apparatus in place of a living animal, I cannot accept that he has refuted the theory that in aortic insufficiency a reflex from the heart to the periphery produces a dilatation of the blood vessels. The occurrence of the collapsing type of pulse, often fairly well marked, in anemia, fever, hyperthyroidism, convalescence, some cases of arteriosclerosis, and in states simply of low

14 Hunt, Reid. The Fall of Blood-Pressure Resulting from the Stimulation of Afferent Nerves, *J Physiol* **18** 382, 1895.

15 Burton-Opitz, Russell. A Text-Book of Physiology, Philadelphia, W. B. Saunders Company, 1920, p. 330.

16 Koster, G., and Tschermak, A. Ueber den Nervus depressor als Reflex-nerv der Aorta, *Arch f d ges Physiol* **93** 24, 1902.

17 Martin, E. G., and Stiles, P. G. Two Types of Reflex Fall of Blood Pressure, *Am J Physiol* **34** 107, 1914.

18 Stewart, H. A. Experimental and Clinical Investigation of the Pulse and Blood Pressure Changes in Aortic Insufficiency, *Arch Int Med* **1** 102 (Jan) 1908.

19 Zollinger, F. Zur experimentellen Pathologie und Therapie der akuten Aorteninsuffizienz, *Arch f Exper Path u Pharmacol* **61** 193 (Sept 30) 1909.

20 MacCallum, W. G. The Changes in the Circulation in Aortic Insufficiency, *Bull Johns Hopkins Hosp* **22** 197 (July) 1911.

vasomotor tone is additional evidence that the *pulsus celer* is not necessarily due to a reflex of blood through the aortic valve Wiggers<sup>21</sup> considers it due to a backward transmission of pressure

In his Harvey Lecture, Muller<sup>22</sup> definitely describes the depressor nerve reflex, and I note that Mackenzie<sup>23</sup> gives credence to the same mechanism as the cause of a dilatation of the peripheral stream bed

#### STATEMENT OF THE THEORY

If the foregoing is a fair, though not necessarily complete picture of the circulatory changes associated with exercise, perhaps the data will enable us to formulate a theory of angina pectoris

Evidence has been given that in the circulatory adaptation to exercise there is a dilatation of the peripheral stream bed, and that this is brought about by the cooperation of the nervous system, probably by a reflex through the depressor nerve fibers of the vagus This acts as a protective mechanism, as it permits the heart to contract without strain A failure of this reflex dilatation of the peripheral arteries is suggested as the essential feature of angina pectoris

#### APPLICATION OF THE THEORY

A necessary effect of the dilatation of the peripheral vessels is, by a more rapid drainage of the blood to the periphery, to lessen the resistance and resulting rise in pressure in the first part of the aorta If the pressure in the start of the aorta is raised this will promptly be felt inside the cavity of the left ventricle, as a higher level of intraventricular pressure will be required before the aortic valve can be opened and the systolic discharge proceed

Applying the theory to the three types of heart disease in which the clinical syndrome, angina pectoris, is prone to occur, one finds pathologic changes of apparent significance In arteriosclerosis the peripheral vessels are known to be less elastic, often much so Also there are degenerative changes in the first part of the aorta and in the myocardium In cardiovascular syphilis there are lesions in the aorta and likewise in the ventricular muscle In chronic hypertensive conditions, both myocardial and aortic changes occur and, for some unknown reason, there is a marked tendency to constriction of the smaller vessels in the periphery

It is quite conceivable that the pathologic alterations, present in the types of heart disease before mentioned, may not only hamper the

21 Wiggers, C J Modern Aspects of the Circulation in Health and Disease, Ed 2, Philadelphia, Lea & Febiger, 1923, p 553

22 Muller, Friedrich Nervous Affections of the Heart, Arch Int Med 1 1 (Jan) 1908

23 Mackenzie, J, cited by Frowde, Henry Diseases of the Heart, Ed 3, London, Oxford University Press, 1913, p 325

operation of the reflex for peripheral dilatation but may make the nerve end plates in the aorta and heart more sensitive to increased pressure. The combination of these two factors may then give rise to the referred pain of angina pectoris.

The anatomy of the nerve tracts involved in the pain of angina pectoris is not the problem of this paper. Mackenzie and others have shown that the pain is of the nature of a referred pain from the lower cervical and upper thoracic segments of the spinal cord. Surgeons<sup>24</sup> have already been successful in removing the pain of angina, by operations devised to separate the heart and aorta from the spinal cord.

Reports on the behavior of the blood pressure during an attack of angina pectoris are rare. Even if the physician is fortunate enough to be present it is not always convenient to make blood pressure studies on the sufferer. Schmidt<sup>25</sup> states that the blood pressure did not fall. Professor Wenckebach, if I recall his words correctly, from his extensive experience states that often the heart during the attack may be noted to be pounding loudly and the blood pressure is increased. That the heart should be "pounding loudly" when the blood pressure is raised is consistent with the observations of Wiggers,<sup>26</sup> who finds that the loudness of the first sound is related to the intracardiac tension developed, and especially to the tension developed before the semilunar valves open. An increase in the intensity of the sound should occur, particularly in those cases in which the level of the diastolic pressure is raised.

In three of his cases Levine<sup>27</sup> measured the blood pressure before and during the attack and gives the following figures: first patient, before, 140 systolic, 90 diastolic, during, 180 systolic, 120 diastolic; second patient, before, 110 systolic, 70 diastolic, during, 164 systolic, 94 diastolic; third patient, before, 162 systolic, 88 diastolic, during, 154 systolic, 78 diastolic. The figures obtained in the first two of these cases, especially the increased diastolic pressure, are consistent with the theory of angina pectoris presented in this paper, but those in the third patient are less easily explained. However, I would point out that

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24 Jonnesco, T. Operative Treatment of Angina Pectoris, *Bull de l'Acad de med, Paris* **84** 93 (Oct 5) 1920, *Presse med* **29** 193 (March 9) 1921, *Bull de l'Acad de med, Paris* **86** 67 (July 19) 1921, *ibid* **86** 208 (Oct 25) 1921, *Presse med* **30** 353 (April 26) 1922. Coffey, W. B., and Brown, P. K. The Surgical Treatment of Angina Pectoris, *Arch Int Med* **31** 200 (Feb.) 1923. Brown, P. K. Cervical Sympathectomy for Angina Pectoris. Report of a Case with Dextral Radiations of Pain, *J A M A* **80** 1692 (June 9) 1923. Wenckebach, K. F. Verbal statement at a clinic given at the Seventy-Fourth Annual Session of the American Medical Association, San Francisco, June, 1923.

25 Schmidt, R. Angina Pectoris, *Med Klin* **18** 6 (Jan 1) 1922, *ibid* **18** 36 (Jan 8) 1922, *abstr J A M A* **78** 930 (March 25) 1922.

26 Wiggers, C. J. Factors Determining the Relative Intensity of the Heart Sounds in Different Auscultation Areas, *Arch Int Med* **24** 47 (Nov.) 1919.

27 Levine, S. A. Angina Pectoris. Some Clinical Considerations, *J A M A* **79** 928 (Sept 16) 1922.

there was a slight fall in *both* the systolic and diastolic pressures, and Levine found but a slight decrease after giving nitroglycerin four times at intervals of but a few minutes each. Addis<sup>28</sup> found that when heart failure was present the pressure curves showed an unusual degree of uniformity in level before and after exercise. It is possible that the factor of cardiac insufficiency entered into Levine's third case to the extent of altering the expected blood pressure figures. More observations are needed on the pressure levels in exercise and during anginal attacks before we can speak with conviction on this point.

In the presence of auricular fibrillation attacks of angina pectoris are a rarity. Thus, in 200 cases of auricular fibrillation Levine<sup>27</sup> did not find a single instance of angina pectoris. This would be in accordance with the theory that I am suggesting, in that it is notorious that when the auricles are fibrillating the blood pressure is poorly maintained (especially when there is a pulse deficit) and hence the nerve end plates in the heart and aorta are not subjected to abnormal strain.

The standard therapeutic measure for an attack of angina pectoris is the administration of the nitrites, amyl nitrite or nitroglycerin. These produce a prompt dilatation of the peripheral vessels and are usually successful in relieving the patient. According to Cushney,<sup>29</sup> this dilatation is the result of an action directly on the smooth muscles of the blood vessels.

Sudden death is known to be the fate of many of those affected by angina pectoris. Allbutt<sup>3</sup> suggests that the fatal result may be due to the stoppage of the diseased heart by the process of vagal inhibition, but in view of what is known of cardiac physiology it seems more probable that the cause lies in the onset of fibrillation of the ventricles. A hint on this problem is found in a paper by Carlson,<sup>30</sup> in which he reports that excessive tension in the heart sometimes sets up delirium cordis, i. e., fibrillation. Carlson was experimenting with the normal heart of animals, and it is plausible that tension far short of excessive might cause the same phenomenon, i. e., the onset of fibrillation,<sup>31</sup> in hearts that are diseased, as are those associated with the syndrome of angina pectoris.

#### SUMMARY AND CONCLUSIONS

The exact lesion, if any, in the heart or the sequence of events occurring in the circulatory system in angina pectoris is unknown.

28 Footnote 10, second reference

29 Cushney, A. R. *A Text-Book of Pharmacology and Therapeutics*, Ed. 7, Philadelphia, Lea & Febiger, 1918, p. 391.

30 Carlson, A. J. Stimulating Action of Tension on the Heart, *Am. J. Physiol.* **18** 149, 1907.

31 The causation of ventricular fibrillation is discussed elsewhere. Reid, W. D. Ventricular Fibrillation Following Ectopic Ventricular Tachycardia. Case Report, *Boston M. & S. J.* **17** 686 (April 24) 1924.

Pathology has failed to disclose the exact nature of angina pectoris

The syndrome, angina pectoris, is a functional condition in the same sense as are the arrhythmias, such as premature beats, etc

It is suggested that the solution of the problem be sought in physiology, both normal and pathologic Angina pectoris is a clinical entity that is absent after death

The adaptations of the circulation to exercise are discussed The evidence is presented, on which is based the belief that during exercise there is a dilatation of the peripheral blood vessels, produced in large part at least by the cooperation of the nervous system, probably by a reflex through the depressor fibers of the vagus nerve

The dilatation of the peripheral stream bed causes a more rapid drainage of blood away from the heart, and lessens the rise of pressure in the first part of the aorta and also the height of that which must be achieved in the left ventricle before the aortic valve can be forced open The heart is thereby enabled to contract without strain

In the three types of heart disease with which the clinical syndrome, angina pectoris, is prone to be associated there are pathologic changes in the first part of the aorta and the ventricular muscle or change in the peripheral blood vessels, or both, which may make abnormal the conditions occurring in the circulation when exertion is undertaken

The sequence of events in angina pectoris may well be a failure of the reflex dilatation of the peripheral blood vessels, which leads to a sudden rise in the pressure in the first part of the aorta and the cavity of the left ventricle, this heightened pressure in turn irritates the local nerve end plates which respond by pain referred to the arm, shoulder, etc

In brief, it is suggested that the essential feature of angina pectoris is a failure of the protective mechanism of reflex dilatation of the peripheral blood vessels

# LABORATORY STUDIES IN EPILEPSY

## I FRACTIONAL GASTRIC ANALYSIS ~

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The frequency of gastric symptoms in epilepsy occurring either as an aura or as a more or less continuous indescribable feeling of distress in the epigastric region prompted the following investigation. Our efforts were limited to a study of the gastric secretion and no attempt was made to supplement this work with roentgenologic examinations.

*Physiology of the Gastric Secretion*—Normal gastric juice obtained from the human stomach free from impurities is a thin, colorless liquid, strongly acid in reaction. The chief constituents are hydrochloric acid and enzymes, pepsin, rennin and possibly lipase. The free acid in gastric secretion is acid which is largely dissociated with the production of a corresponding amount of free hydrogen ions. The combined acid is that which is bound with the protein material of the gastric juice. The gastric juice is secreted by tubular glands imbedded in the mucous membrane of the stomach. The mouths of these glands can be seen as innumerable depressions studding the gastric mucosa everywhere. These glands differ in structure and function in different regions of the stomach. Two types may be differentiated: (1) The cardiac gland, the lumen of which is lined by epithelial cells cuboidal in shape and of two varieties: *a*, central cells which border the lumen of the tubule and *b*, larger oval-shaped parietal cells lying just beneath the gland wall. Each parietal cell appears to be surrounded by a delicate network of canals which eventually open into the lumen of the gland by means of a small cleft, and (2) the pyloric gland, lined by epithelial cells exclusively of the chief or central type. These glands secrete an alkaline liquid containing the digestive enzymes (pepsin and rennin) and, according to Edkins and Starling, a hormone which excites the secretion of the gastric juice.

It is generally conceded that the parietal cells of the gastric glands are concerned exclusively with acid secretion. Microchemical reactions show them to be very rich in chlorids and a portion of the stomach lacking these cells (pyloric region) has an alkaline secretion. The parietal cells are most abundant in the middle or prepyloric region of the stomach, scanty in the fundus and entirely absent in the pyloric portion.

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\* The studies described in this and subsequent papers were made at the U S Veterans' Hospital No 81, Bronx, New York City. Published through the courtesy of Gen Frank T Hines.

Grutzner<sup>1</sup> states that normally the food in the fundus becomes first impregnated with pepsin, and then as it approaches the prepyloric region of the stomach receives its hydrochloric acid constituent. Harvey and Bensley,<sup>2</sup> in their investigations to ascertain the exact point of formation of hydrochloric acid in the gastric juice, state that free acid is found only on the internal surface of the stomach or in the neck of the glands. The parietal cells themselves are alkaline in reaction. The ultimate sources of the chlorine in the hydrochloric acid are the chlorides in food and the neutral chlorides (sodium chlorides) of the blood,<sup>3</sup> which are formed into some intermediate compound by the parietal cells and yield free hydrochloric acid only after the secretion reaches the neck of the gland. If chlorides in the blood are reduced by their elimination from the food for a sufficient length of time the gastric juice will no longer contain acid.

*The Nervous Control of Gastric Secretion*—The secretion of gastric juice as effected by the epithelial cells (and in part by the gastric blood vessels) is under definite nervous control. The efferent secretomotor nerves are contained in the vagus trunk. These fibers originate in the floor of the fourth ventricle<sup>4</sup> and terminate in the stomach wall around dendrites of nerve cells, whose ganglionic fibers reach the secretory epithelial cells. There are also vasomotor nerves which vary the caliber of the gastric blood vessels, and so indirectly control the flow of gastric juice. These fibers arise from cells situated in the lateral horn of the gray matter in the thoracic region of the spinal cord, and pursue their course downward entering the celiac ganglion forming synapses with dendrites of nerve cells which finally end in the nonstriated fibers of the gastric arterioles. This latter nervous mechanism is under the control of the vasomotor center in the medulla. The presence of true secretory fibers in the vagus can be demonstrated by section of this nerve and stimulation of the peripheral cut end. This causes secretion of gastric juice, after a latent period of several minutes, due to the presence also of some inhibitory fibers being stimulated simultaneously with the secretory fibers. It is evident therefore that the vagi can stimulate as well as inhibit the flow of gastric juice, and thus constitute the chief efferent secretory pathway between the central nervous system and the stomach.<sup>5</sup> The stomach will continue to secrete some gastric juice even after division of all of its nerves (vagus and splanchnic).

1 Grutzner. *Arch f d ges Physiol* **106** 463, 1905 (quoted from Howell)

2 Harvey, B C H, and Bensley, R R. *Biol Bull* **23** 225, 1912

3 Howell, W H. *Text Book of Physiology*, Philadelphia, W B Saunders Company, 1918, p 780

4 Brubaker, A P. *Text Book of Human Physiology*, Philadelphia, P Blakiston's Son & Company, 1922, p 178

5 Burton-Opitz, R. *Text Book of Physiology*, Philadelphia, W B Saunders Company, 1920, p 929

This viscus therefore has a local reflex mechanism and can be considered a typical autonomic organ, subject to constant influence by the higher nerve centers. The afferent pathways carrying impulses to the secretomotor and vasomotor cells lead from the cerebrum and oral mucosa.

The physiology of gastric secretion has been gone into in some detail because it gives one a somewhat clearer understanding of the unusual findings noted in our series of epilepsy cases.

In carrying out these studies the following procedure was used:

#### METHOD OF PROCEDURE

The patient reached the laboratory at about 9 a. m., after fasting all night. A Rehfuß (modification of the Einhorn) tube was passed and the fasting contents extracted. The patient then swallowed a glass of water without disturbing the tube or else the water was injected into the stomach through the tube by means of a syringe. Approximately 15 cc of gastric fluid was then extracted every fifteen minutes for a period of two hours. Water was used in preference to the usual test meal because it has the advantage of demonstrating any food rests, is quite as great a stimulant to gastric juice as the Ewald test meal, contains no element which might give rise to lactic acid and is easily administered to irritable patients. The stimulatory power of water in the stomach of lower animals was shown by Heidenham<sup>6</sup> and later by Sanotskii.<sup>7</sup> Wells and Hawk<sup>8</sup> made similar studies on the human stomach. It was found that ordinary water, cold (10.5 C) or warm (50 C) was a very strong gastric stimulant, sometimes giving rise to an acidity of over 100 in less than twenty minutes. Even as small an amount as 50 cc of water has a pronounced stimulatory effect. Increased acidity is apparently accompanied by increased peptic activity, which leads one to conclude that both the acid and pepsin secreting cells are stimulated. The average acidity after water stimulation was 77. Freshly secreted human gastric juice possesses an acidity of from 0.4 to 0.5 per cent (the figures given below can be converted to percentage by multiplying by the factor 0.00365). This initial high acidity is normally lowered to the so-called "optimum acidity" of from 0.15 to 0.2 per cent (that acidity which seems to promote the most effective pepsin activity and therefore proteolytic digestion) by the regurgitation of alkaline fluids from the intestine (biliary, pancreatic and intestinal secretions). Bolydroff<sup>9</sup> terms this "the automatic regulation of gastric acidity."

In order to more clearly understand the figures given in the tables, the following brief summary of fractional studies of gastric acidity is appended as outlined by Rehfuß, Bergeim and Hawk.<sup>10</sup> These investigators describe three types of curve obtained by fractional analyses:

*Isosecretory Type*—The total acidity rises steadily to about 60 within one-half to one hour. This is followed by a gradual decline, reaching the initial acidity at the end of about two hours. This curve is usually unbroken and the high point is rounded.

6 Heidenham, R. Arch f d Ges Physiol **19** 148, 1879.

7 Sanotskii. Arch d sc biol **1** 588, 1892.

8 Wells, H. G., and Hawk, P. B. Proc Am Soc Biol Chemists, **2** 23, 1910.

9 Bolydroff. Quoted from Hawk, P. B. Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Company, 1922, p. 153.

10 Rehfuß, M. E., Bergeim, O., and Hawk, P. B. Gastro-Intestinal Studies, J. A. M. A **63** 909 (Sept 12) 1914.



TABLE 1—*Gastric Acidity Figures Obtained in Fifty-Three Cases of Epilepsy*

Case	Inst- ing		15 Min		30 Min		45 Min		60 Min		75 Min		90 Min		105 Min		120 Min		Remarks
	F*	T*	F	T	F	T	F	T	F	T	F	T	F	T	F	T	F	T	
1	30	52	28	46	42	58	50	65	50	64	52	67	56	71	56	72	60	73	
2	0	18	0	8	0	6	0	8	0	6	0	16	0	10	0	12	0	12	April 4, 1923
2	0	12	0	6	0	8	0	16	10	28	5	22	0	17	0	11	0	12	May 22, 1923
3	0	14	0	10	0	8	0	14	0	14	12	26	18	32	16	34	26	40	
4	32	46	6	20	33	48	38	52	46	85	56	76	53	72	48	68	48	54	Aug 25, 1922
5	0	18	0	68	16	70	18	68	32	72	28	86	32	80	32	80	30	80	July 10, 1922
5	0	8	0	7	0	10	0	8	0	10	0	10	0	8	0	8	0	10	June 19, 1923
6	0	16	0	26	8	32	22	46	18	54	26	68	40	46	42	64	28	56	
7	0	10	0	8	0	12	0	15	0	15	0	17	0	0	0	24	0	15	
8	0	14	3	14	25	36	26	34	20	42	32	42	58	51	28	39	40	52	April 19, 1923
9	0	10	0	4	0	6	0	7	0	11	0	10	0	10	0	8	0	12	Bile present in all but F and 1
10	0	20	8	16															Seizure Dec 14, 1922
11	0	20	4	16	2	16	12	24	18	32	14	32	30	48	38	52	34	48	
12	0	12	10	18	26	35	14	23	13	25	18	32	26	38	24	36	28	36	
13	0	10	0	20	0	14	0	18	0	18	0	15	0	20	0	18	0	18	
14	40	56	28	36	30	40	34	44	20	42	16	34	28	48	20	26	16	30	
15	36	50	10	22	30	45	40	65	25	85	20	60	10	70	50	62	60	75	
16	60	80	24	36	66	88	64	82	80	98	92	110	64	78	92	110	94	108	
17	0	8	0	14	0	10	0	14	0	12	0	12	0	12	0	14	0	12	
18	28	46	10	22	32	50	46	64	64	80	68	82	60	74	57	74	60	72	
19	10	40	30	50	30	50	20	50	20	40	40	50	50	70	60	100	60	100	Another ½ hour showed persistence from 60-100 July 13, 1922
20	0	15	0	35	20	25	10	35	20	30	10	35	25	40	15	25	15	20	
21	0	17	10	18	13	22	12	23	10	20	27	36	24	36	25	36	0	10	April 20, 1923
22	20	30	24	50	26	52	36	64	46	86	56	82	56	80	62	80	48	62	
23	0	22	5	16	10	45	30	70	32	80	10	36	14	38	8	20	8	22	
24	0	10	0	18	0	20	20	36	30	42	10	25	14	26	24	36	24	36	
25	30	48	28	36	34	42	44	52	44	56	40	56	44	62	48	62	52	66	
26	14	32	22	38	46	58	62	74	76	92	80	94	70	83	64	78	64	76	
27	0	20	10	16	24	32	26	34	26	42	32	44	38	52	38	52	50	64	
28	32	52	10	16	16	22	16	32	30	40	32	44	32	46	20	40	12	34	Feb 23, 1923

\* F, free acidity, T, total acidity

TABLE 1—*Gastric Acidity Figures Obtained in Fifty-Three Cases of Epilepsy—(Continued)*

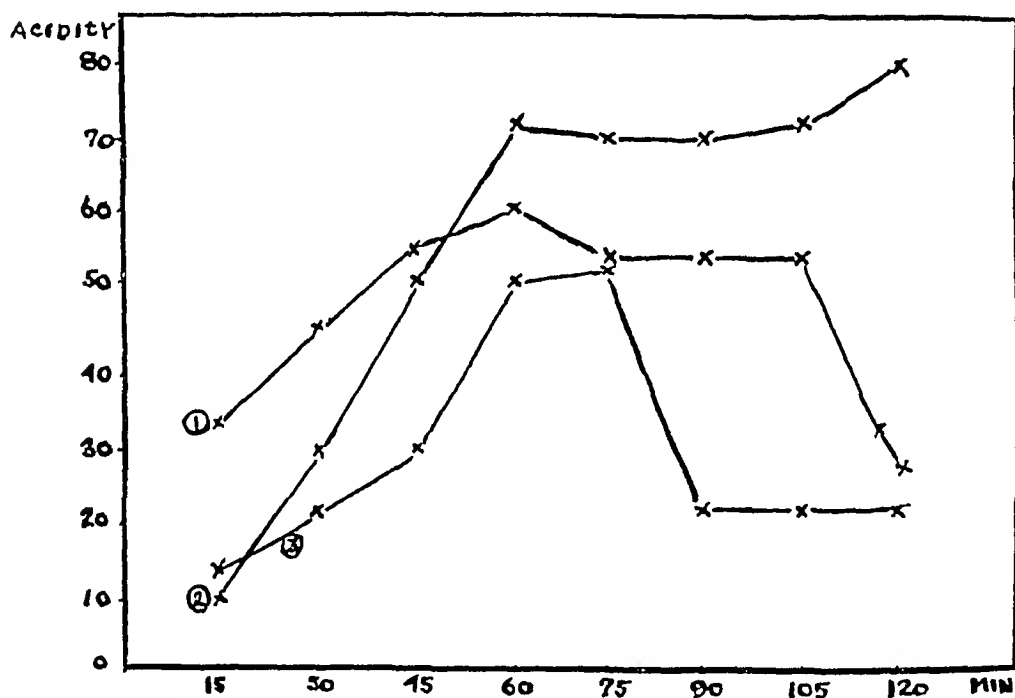
Case	First- ing		15 Min		30 Min		45 Min		60 Min		75 Min		90 Min		105 Min		120 Min		Remarks
	F*	T*	F	T	F	T	F	T	F	T	F	T	F	T	F	T	F	T	
29	46		6		20		12		32		10		20		27		26		April 16, 1923
	82		14		34		27		45		24		36		44		41		
30	0		0		4		4		4		0		16		0		16		
	16		10		16		18		18		12		30		18		28		
31	0		0		0		0		0		0		0		8		10		
	12		12		8		10		10		10		10		16		26		
32	0		0		42		32		25		14		0		0		0		
	10		8		52		43		35		26		14		10		15		
33	0		0		0		5		18		36		34		34		24		
	16		10		12		17		30		48		44		44		34		
34	0		8		28		38		40		40		36		38		60		Feb 15, 1923
	10		14		38		50		52		52		48		50		74		
35	0		4		2		8		6		4		4		10		24		
	10		8		12		16		16		16		16		28		40		
36	0		0		0		0		0		0		0		0		No g J		Feb 19, 1923
	10		8		8		8		10		10		10		10		obtained		
36	0		0		0		0		0		0		0		0		0		Mar 28, 1923
	14		15		10		8		10		10		14		18		18		
37	22		0		0		0		0		20		0		36		40		
	44		12		12		12		20		36		16		48		52		
38	15		0		0		20		35		44		55		48		25		
	30		12		15		35		50		56		68		58		35		
39	0		4		4		18		26		24		26		14		30		
	16		14		20		36		46		58		56		62		56		
40	13		0		27		40		40		30		30		30		29		
	30		8		36		52		52		43		42		40		39		
41	40		38		56		56		60		75		70		74		33		
	54		45		66		70		75		75		86		89		53		
42	56		10		50		62		80		68		40		66		74		
	72		16		57		70		85		77		50		74		83		
43	15		20		28		32		30		38		46		50		43		
	25		27		40		54		67		56		53		66		58		
44	0		0		0		0		0		0		0		0		0		
	12		8		22		18		13		14		15		10		18		
45	0		14		21		35		11		52		31		55		66		89 94
	11		22		30		64		37		60		45		65		73		
46	0		10		22		40		37		39		48		38		44		
	22		16		32		53		47		52		56		49		54		
47	0		16		38		45		38		47		54		56		38		
	17		20		42		50		48		55		64		64		45		
48	3		3		28		46		58		42		44		51		65		
	18		14		38		56		71		54		56		63		77		
49	50		23		45		51		43		51		45		38		30		
	76		32		50		62		59		61		52		43		40		
50	48		12		28		38		48		56		46		40		44		
	68		22		46		54		62		72		60		58		58		
51	32		22		40		36		34		30		32		34		58		
	52		30		52		48		44		42		46		54		72		
52	0		0		4		16		16		20		26		24		34		
	18		18		18		24		20		30		32		38		46		
53	40		19		28		39		48		56		56		70		74		
	53		25		36		46		56		63		63		78		85		
54	20		40		70		50		50		30		10		10				
	30		60		70		80		50		40		40		30				
55	24		12		20		24		22		20		24		26		28		
	44		22		30		32		32		32		36		36		42		
56	0		4		16		28												
	26		26		50		76												
57	4		0		39		35		30		17		30		27		30		
	30		16		57		50		46		35		40		46		49		

\* F, free acidity, T, total acidity

*Hypersecretory Type*—There is a rapid increase in acidity with a high point of from 70 to 100 or over, either sustained or abrupt. The decline to initial acidity is slow or does not occur at all within two hours.

*Hyposecretory Type*—Here there is a slower increase in acidity than in the isosecretory type with a high point of from 40 to 50. Return to initial acidity occurs within from two to two and one-half hours.

Bearing in mind the foregoing description of the physiology of gastric secretion and the types of curve obtained by fractional gastric studies in normal human beings, we may now proceed to a consideration of the results obtained in epileptics. The following table gives in detail the figures obtained in a series of fifty-three cases. We were successful



Types of curve obtained by fractional gastric analysis: (1) Isosecretory, (2) Hypersecretory, (3) Hyposecretory. Solid lines indicate total acidity. Free acid curves have been omitted for the sake of simplicity. They follow in the main the total acid, being somewhat lower throughout.

in repeating our studies in only six cases because of the peculiar temperament usually encountered in these patients.

It will be seen that eight patients (Case Nos. 2, 5, 7, 9, 13, 17, 36 and 44) exhibited complete absence of free hydrochloric acid in the fasting stomach and throughout a period of two hours after the ingestion of water. Three of these eight cases were checked up by repeating the gastric analysis (2, 5, 36). Patient No. 2 (April 4, 1923) was re-examined on May 22, 1923, with the same results. Patient No. 5 showed, on July 19, 1922, absence of free acid only in the fasting and

fifteen minute specimens, but a second analysis on June 19, 1923, showed absence of free hydrochloric acid in the fasting contents and all specimens collected within two hours. It might be well to note that this patient was under our close observation during all this time and had undergone very rapid and marked mental deterioration. Patient No 36 showed no change on two separate examinations (Feb 19 and March 28, 1923). In all of the above eight patients the total acidity remained uniformly low in all specimens, the average acidity being 12. Another case which might be added to these eight patients is No 31, in whom no free hydrochloric acid was found until the one and three-quarter hour extraction and even then only a trace was present. Patient No 3 showed similar findings until the one and one-quarter hour extraction was reached. Patient No 30 showed practically complete absence of free acid in all specimens except the one and one-quarter and one and three-quarter hour extractions. Here it is rather difficult to explain the zig-zag acidity curve obtained after one and one-quarter hours (0 to 16 to 0 to 16 again). Somewhat similar results were obtained in Cases 32 and 37. The former patient showed an initial absence of free acid followed by a rapid rise to 42 in one-half hour and decline to zero within the following hour, the absence of free acid persisting to the end. The latter (Case 37) showed a fasting free acidity of 22, followed after the ingestion of water by no free acid for a period of one and one-half hours (except for an acidity of 20 in the 75 minute extraction). Patient No 3 showed practically complete absence of free acid in all specimens except the one and one-half hour extraction. Sixteen patients (Cases 6, 8, 11, 20, 23, 24, 32, 33, 34, 35, 38, 39, 48, 52, 56 and 57) showed complete absence or only very slight traces of free acid in the first two or three extractions.

One patient (10) was examined on three different occasions. The first time only the fasting and fifteen minute extractions were made, the patient then suddenly going into a seizure. The figures for free acidity were 0 for the fasting specimen and 8 for the fifteen minute specimen. Exactly similar results were obtained on two subsequent occasions when the patient was feeling comparatively well. This point is brought out in order to show that in this case at least, examination of the gastric juice just before a seizure showed no change so far as the acidity was concerned.

For purposes of comparison Table 2 is shown, giving gastric acidity figures for other patients in the hospital. None of these figures are taken from patients having a doubtful or definite diagnosis of epilepsy.

It is surprising to note that seven patients show complete or almost complete absence of free hydrochloric acid in all specimens (Cases 4, 27, 28, 30, 31, 32, 33 and 35). In looking up the clinical records of these latter patients the following interesting data were obtained

TABLE 2—Control Figures Gastric Acidity Estimations Made on Thirty-Seven So-Called Nonepileptic Patients

Case	Fast ing			15 Min		30 Min		45 Min		60 Min		75 Min		90 Min		105 Min		120 Min		Remarks	
	F	T	*	T	T	F	T	F	T	T	T	F	T	F	T	T	T	T	T		
1				68		52		5		0		34		10		44		50			
					82		62		34		20		52		35		54		60		
2	0			0		0		17		18		32		27		35		38			
		15			8		10		27		28		46		41		49		56		
3	22			0		0		16		26		44		22		6		0			
		40			20		28		46		48		62		40		24		26		
4	3			2		2		2		0		0		0		0		0			
		15			12		12		15		12		14		14		15		14		
5	0			0		30		32		26		12		14		20		27			
		18			22		42		46		40		28		30		34		42		
6	0			8		14		10		0		4		6		0		0			
		18			18		30		28		20		22		24		16		14		
7	16			6		16		24		54		36		36		26		20			
		32			10		20		32		60		50		48		34		20		
8	20			0		18		32		20		14		12		14		20			
		38			10		26		44		34		27		26		30		35		
9	30			14		24		32		38		44		46		52		64			
		50			20		26		38		44		50		58		66		76		
10	28			6		10		10		10		16		26		0		20			
		38			14		18		16		20		26		36		10		34		
11	32			12		14		12		8		10		4		0		0			
		44			18		20		22		22		22		20		16		12		
12	20			8		26		39		36		33		27		35		40			
		48			20		37		52		56		58		39		48		54		
13	16			12		10		10		26		46		40		32		22			
		20			16		16		18		36		60		54		44		38		
14	52			18		0		20		12		16		10		8		0			
		64			28		20		50		30		32		24		22		15		
15	36			0		10		13		28		34		20		28		36		Nos 7 and 8 continue	
		48			12		17		22		38		42		32		36		45		
16	12			4		0		0		0		4		34		26		20			
		30			22		12		14		14		20		50		40		36		
17	20			14		30		22		26		13		29		20		56			
		25			22		36		36		46		32		45		28		71		
18	14			12		14		14		28		13		32		13		16			
		34			24		24		28		40		30		44		32		22		
19				38		42		14		20		18		8		18		18			
					54		62		30		36		34		20		32		30		
20	40			0		0		20		5		28		34		28		38			
		52			20		22		44		30		52		60		44		58		
21	0			16		52		58		38		40		60		28		44			
		20			28		62		74		50		60		72		34		54		
22	8			8		16		30		4		4		16		18		30			
		28			13		22		38		14		17		28		31		42		
23	0			12		36		48		46		36		38		38		20			
		0			23		52		61		58		50		53		53		35		
24	20			14		18		24		16		26		32		20		32			
		34			22		26		30		26		34		42		34		44		
25	0			0		32		34		6		0		16		18					
		12			12		42		48		20		16		28		20				
26	20			5		30		30		40		40		30		40		40			
		35			10		35		43		50		55		55		50		50		
27	0			0		0		0		0		0		0		0		0			
		20			6		8		10		12		20		20		20		20		
27	0			0		0		0		0		0		0		0		0		June 19, 1923	
		14			8		8		20		12		12		10		10		10		
28	0			0		0		0		0		0		0		0		0			
		15			8		10		12		15		18		18		15		12		
29	0			0		0		10		12		24		15		11		17			
		15			6		8		18		22		37		31		26		31		

\* F, free acidity, T, total acidity

TABLE 2—Control Figures Gastric Acidity Estimations Made on Thirty-Seven So-Called Nonepileptic Patients—(Continued)

Case	Fast- ing		15 Min		20 Min		45 Min		60 Min		75 Min		90 Min		105 Min		120 Min		Remarks
	F	T	F	T	F	T	F	T	F	T	F	T	F	T	F	T	F	T	
30	0		0	18	0	19	0	35	0	42	0	30	5	35	7	39	15	40	22 70
31	0		0	8	0	6	0	6	0	10	0	10	0	10	0	10	0	10	
32	0		0	6	0	8	0	10	0	10	0	8	0	12	0	16	0	22	
33	0		0	8	0	14	0	18	0	14	0	16	0	16	20	44	8	24	
34	0		0	8	0	8	34	46	38	52	15	25	17	30	20	36	6	22	
35	0		0	6	0	10	0	10	0	10	0	12	0	10	0	10	0	18	
36	10		11	19	14	18	18	26	20	33	26	34	26	34	40	50	36	46	
37	0		0	14	20	31	20	32	21	33	27	44	34	49	36	51	58	72	

\* F, free acidity, T, total acidity

#### REPORT OF CASES

CASE 1 (Patient 4)—The patient, a man, while on military duty on the Mexican border (about 1917), was thrown from his horse and "lay unconscious for several hours." On recovery he suffered from pains in the back and passed bloody urine. In December, 1921, while mounting a flight of stairs, he fell backward and bruised his head, remaining unconscious for twenty minutes. He often felt dizzy and weak being compelled to hold on to things in order to keep from falling. At such times his heart thumps and seems to stop, the patient feeling as if he were being pulled over backward.

*Clinical Diagnosis*—Mild secondary anemia

*Relizant Examinations*—The blood Wassermann test was negative. The urine was normal. Blood-hemoglobin 88 per cent (Dare), erythrocytes, 4,100,000 per cubic millimeter, leukocytes, 7,800 per cubic millimeter, polymorphonuclear neutrophils 66 per cent, small lymphocytes 26 per cent, large lymphocytes, 6 per cent, transitional 1 per cent, eosinophil 1 per cent.

*Epicrisis*—The blood count hardly seems to account for the absence of free acid or the nervous symptoms. The history of a fall followed by a period of unconsciousness and subsequent attacks of dizziness, unconsciousness and cardiac distress are very suggestive of epilepsy.

CASES 2, 3, 4, 5 and 6 (Patients 27, 28, 30, 31 and 33)—Portrayed many of the characteristics seen in "petit mal" attacks and interval periods of long standing epilepsy. Thus patient 27 experienced attacks of cardiac pain and "smothering" associated with gastric distress. Patient 28 was afflicted with insomnia, periods of cardiac and gastric distress, peculiar periods of numbness of the left side of the body, headache, a frequent feeling of falling into space, deterioration of memory, inability to concentrate and tiring after light exercise.

Patient 30 complained of inability to concentrate and a feeling of gastric distress associated with "nervousness and stiffness of the legs." He also displayed the peculiar antagonistic attitude often seen in epilepsy.

Patient 31 complained of insomnia and frequent spells of excitement lasting a few minutes and associated with headache and precordial pain. Palpitation of the heart, easy tiring after exercise and inability to concentrate were also present. In this case electrocardiographic examination by Dr. H. Mann revealed the presence of auricular fibrillation. The blood Wassermann was positive. Blood

pressure, 150 systolic, 105 diastolic Metabolic rate, minus 15 per cent Roentgen-ray examinations of the teeth gave evidence of periapical abscesses of the upper left first and second molars and upper right first molar

Patient 33 complained of "nervous spells" associated with insomnia, irritability, headache and attacks of dizziness

Patients 27, 28, 30 and 33 gave no physical or laboratory evidence suggesting and explanation of their symptoms

CASE 7 (Patient 32)—The chief complaints of this patient, a man, were nervousness and pains in the gastric and cardiac regions At 6 years of age the patient fell down a flight of stairs and injured his head Since then he had been unreasonable in his demands, lies and loses his temper very easily He "shakes" when excited These symptoms were greatly aggravated following an aeroplane raid in 1918

*Clinical Diagnosis*—Constitutional psychopathic inferiority

*Relevant Examinations*—The blood and spinal fluid Wassermann tests made at a Red Cross Hospital abroad were positive (patient's statement, report could not be confirmed as records were not available) The patient received arsphenamin injections The blood and spinal fluid examinations made by this laboratory were entirely negative (including Wassermann test made after provocative arsphenamin injection) Psychometric examination revealed an equivalent age of 16 years and 3 months (actual age 24 years) Intellectual quotient 101, therefore there was no mental deficiency

*Etiology*—Nervousness, pains in the region of the stomach and heart, "shaking spells" and an unusual mental trend should be regarded in the light of a history of a fall on the head and onset of symptoms following shock associated with an aeroplane raid While one should be careful not to make facts fit theory, yet the history and symptoms of this patient resemble those found in many cases of epilepsy It is quite usual, in our opinion, for patients to overlook symptoms following a fall on the head during childhood, and to associate the present trouble with an incident occurring during military service

CASE 8 (Patient 35)—The patient, a man, twenty-five years ago received a wound on the left frontal region of the skull He was unconscious for several days and hospitalized for several months, during which time there was almost a complete loss of memory In 1917 he began to experience dizzy spells and often fell unconscious for periods lasting about five minutes, during which time there were convulsive movements, frothing at the mouth and loss of sphincter control He suffered from dyspnea on exertion and tired easily He often felt nauseated after meals

*Clinical Diagnosis*—Anxiety neurosis An old gunshot wound on the frontal region of skull

*Relevant Examinations*—Physical examination revealed at 2.5 cm oval depression in the left frontal region of the skull extending down to the inner table The vision in the left eye was 2/200 The left fundus could be seen with a minus 14 lens The disc was pale, retina and choroid were much thinned out allowing the sclera to show through, especially in the lower quadrant Blood pressure, 140 systolic, 75 diastolic The urine analysis was negative Roentgen-ray examination of the teeth revealed the presence of several peri-apical abscesses The blood count was normal Wassermann reaction negative

*Etiology*—The history of trauma, taken in conjunction with the finding of an actual bony defect in the skull, was associated with phenomena usually observed in epilepsy

#### COMMENT

All of the data above presented merely constitute our observations on fifty-three epileptics and thirty-seven other cases chosen at random as controls Of the epilepsy group, eight cases (15 per cent) showed complete absence of free hydrochloric acid in the fasting stomach, and

for a period of two hours following the ingestion of a water test meal. Six others (11 per cent) showed similar results, except that the absence of free hydrochloric acid fell somewhat short of the two-hour period. Sixteen cases (30 per cent) showed absence or only slight traces of free acid in the first two or three specimens. Of the thirty-seven so-called nonepileptic control group, seven (19 per cent) showed complete absence of free hydrochloric acid in all specimens. Five (13 per cent) showed absence of free hydrochloric acid in the first two or three specimens. In our series no deductions could be drawn from the total acidity curves. Qualitative and quantitative ferment studies were also made on all specimens, but no conclusions could be reached because of the variability found in our control tubes. We found, for example, that quantitative and sometimes even qualitative tests for pepsin by the use of Mett tubes were absolutely inaccurate. The same batch of albumin (coagulated in a water bath at one time) used on identical specimens of filtered gastric juice gave different results. Sometimes at the

TABLE 3—*Comparison of Free Acidity Curves Obtained in Epilepsy and Control Groups*

	No Free Acid in 2 Hour Period, per Cent	No Free Acid in Period a Little Less Than 2 Hours, per Cent	Absence or Trace of Free Acid in Fasting, 15 and 30 Minute Specimens, per Cent
Epilepsy group	15	11	30
Control group	19*	0	13

\* On further investigation most, if not all, of these cases could with a reasonable degree of certainty be considered epileptic.

end of twenty-four hours we would get no digestion at all in one tube, and from 5 to 7 mm. in another, both tubes containing the same gastric juice.

In considering the foregoing figures, due regard should be had for the opinion of many gastro-enterologists who attach comparatively little importance to gastric acidity titrations. The cases cited in our series gave evidence of anacidity over a long period of examination. We cannot disregard these observations, especially when taken in conjunction with suitable controls. Kopeloff,<sup>11</sup> in an interesting study on the Rehfuß fractional method of gastric analysis, shows the great variations one may obtain in specimens withdrawn in rapid succession three-quarters of an hour after the ingestion of a test meal. He also showed that specimens of gastric juice drawn simultaneously through three different tubes from the stomach of one individual differed widely in the degree of acidity, depending on the location of the bucket. These observations can readily be explained by our knowledge of gastric

<sup>11</sup> Kopeloff, Nicholas. Variations in Aliquot Fractions of Gastric Contents, Arch. Int. Med. 30: 118 (July) 1922.



physiology We avoided such sources of error by withdrawing large fractions, and keeping the tube so far as possible in one place

Theoretically, absence of free hydrochloric acid may be the result of one or more of the following factors (1) Overactivity of the pyloric glands which secrete an alkaline fluid, (2) absence of chlorids from the food, thereby impoverishing the blood and removing the source of manufacturing material for hydrochloric acid from the parietal cells, (3) destruction of parietal cells (by caustics, malignancy, etc), (4) excessive regurgitation of alkaline juices from the small intestine, (5) overstimulation of inhibitory fibers in the vagus, (6) destruction of the secretory fibers in the vagus, (7) destruction of the cells of origin of the secretory fibers which lie in the floor of the fourth ventricle or of the synapses and fibers involved in the autonomic control of gastric secretion, (8) pathologic lesion of vasomotor fibers, associated cells and synapses lying in the gray matter of the thoracic region of the spinal cord or in the celiac ganglion, (9) severe anemia, (10) technical error, whereby the bucket is located in the duodenum instead of in the stomach

Let us consider these factors in the order above mentioned Overactivity of the pyloric glands is probably not a great factor, as it would possibly require a great quantity of this secretion to neutralize a gastric acidity of from 0.2 to 0.5 per cent

Absence of chlorids from the food and subsequent impoverishment of the blood was not a factor in our cases, as shown by chemical analysis of the blood and definite control of diet

Destruction of the parietal cells, if great enough in extent, would lead to absence of free hydrochloric acid This certainly seems to be true of invasive carcinomas of the prepyloric or cardiac regions

The absence of free hydrochloric acid in severe primary or secondary anemias is probably associated with the poor quality of blood brought to the parietal cells There may be an intravascular chlorid retention, in the effort to keep the fluid content of the blood normal Percentage variations may therefore not be revealed by chemical analysis of the blood

Technical errors are probably not a factor, as tubes passed a definite distance have been shown to be located in the stomach for several hours Moreover, this would hardly account for the absence of free acid in all specimens with no bile present

With regard to possible defects in the nervous control of gastric secretion, one must regard as highly probable the presence in some epileptics of a gliosis, a gliomatous process or other pathologic lesion in the regions of the floor of the fourth ventricle, the gray matter of the thoracic spinal cord, celiac ganglion or elsewhere in the vagal or vasomotor pathway Two cases which came to necropsy have so far revealed

no definite brain pathologic changes Vanderhoof<sup>12</sup> reports a series of twenty-nine cases of achylia gastrica, associated with a combined sclerosis of the spinal cord Fourteen of these patients had pernicious anemia

Hurst and Bell<sup>13</sup> report eight cases of combined spinal sclerosis, showing absence of free hydrochloric acid by the fractional method These observations are very interesting, especially if considered in the light of certain theories as to the causation of epilepsy On this point one can do no better than consult the masterly work of Brown-Sequard<sup>14</sup> In a series of careful experiments on animals and human beings he concludes that an injury to the spinal cord may be the cause of an epileptiform affection He cites many instances of pathologic changes found in the spinal cords of epileptics at necropsy (Clot, Olivier d'Angers, Bouchet and Cazanviele, Foiget, Jendriss and others) He even goes so far as to have grave doubts that the seat of trouble in any epileptic can primarily lie in the cerebral lobes If certain or all cases of true epilepsy should really be due to sclerotic changes in the spinal cord, the lesions would in all probability involve the lateral horns of the gray matter in or above the thoracic region of the spinal cord There is a possibility that the small hemorrhages occurring in the eyelids and skin elsewhere, due to pathologic conditions associated with an attack (to be described in a subsequent paper), may also occur in any of the regions above described and eventually lead to a replacement gliosis Defects in the central nervous control of gastric secretion are more likely than local lesions if one is to consider our gastric findings of significance in epilepsy

#### CONCLUSIONS

1 Complete absence of free hydrochloric acid in the fasting and subsequent specimens obtained over a period of two hours was found in 15 per cent of our epileptic cases Almost complete absence of free acid was found in another 11 per cent, thus making a total of 26 per cent

2 Of the so-called "nonepileptic" control group, 19 per cent showed complete absence of free acid, and further investigation made it seem quite likely that all of these patients were epileptic

3 The absence of free acid in one patient closely observed for more than a year, seemed to be associated with rapid deterioration

4 In one patient, the absence of free acid did not seem to be associated with the onset of an epileptiform attack

5 The total acid curve remained uniformly low in all cases of absence of free acid

12 Vanderhoof, Douglas The Etiologic Relation of Achylia Gastrica to Combined Sclerosis in the Spinal Cord, *Arch Int Med* **32** 958-971 (Dec) 1923

13 Hurst, A F, and Bell, J R *Brain*, **45** 266 (Oct) 1922

14 Brown-Sequard, E *Boston M & S J* **54** 55, 1856

I have endeavored in this paper merely to present a record of my observations. The absence of free acid may not be pathognomonic of epilepsy, but in my opinion this fact seems worthy of further investigation. Periodic gastric analyses of epileptics and more careful investigation of all neuropsychiatric cases showing anacidity are suggested.

# EXPERIMENTAL AND CLINICAL SIGNIFICANCE OF THE CHOLESTEROL CONTENT OF BILE

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AND

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It would appear superfluous to make a review of the vast amount of literature, which has appeared during the last few years, concerned with nonsurgical drainage of the gall tract, following Lyon's<sup>1</sup> original and subsequent expositions on the subject

We are of the opinion (after the experience gained by one of us in draining over 1,500 gall tracts) that the bile, when obtained by this method, does appear in more or less definite fractions, corresponding to Lyon's "A," "B" and "C" bile. Where this does not occur in a patient who is "tube broken," there is usually some pathologic change to account for it, if the technic has not been faulty

In an excellent paper which appeared recently, Rous and McMaster<sup>2</sup> demonstrated that the gallbladder is the only structure in the gall tract which can normally concentrate bile. They studied the ability of the gallbladder to concentrate bile, using as a criterion the pigment strength of a sample collected from an hepatic duct branch. Gallbladders (five), which had been previously emptied, concentrated bile coming into them on an average of 7.1 times in twenty-four hours. Gallbladders (seven), left distended with bile of known constitution and receiving in addition fresh increments from the liver, concentrated the secretion on an average 6.4 times in twenty-four hours. They have shown that normally the ducts do not have the faculty of concentrating bile, but on the contrary dilute it.

Granting that the gallbladder is the only structure in the biliary tract which concentrates bile, in order to demonstrate that the "B" fraction of bile is derived in large part from the gallbladder, we must prove that

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\* From the Gastroenterologic Clinic, Graduate School of Medicine, University of Pennsylvania

\* Read before the Interurban Surgical Society at Philadelphia, May 15, 1923

1 Lyon, B. B. V. Diagnosis and Treatment of Diseases of the Gallbladder and Biliary Ducts, *J. A. M. A.* **73** 980 (Sept 27) 1919, *M. Clin. N. Am.* **3** 1253 (March) 1920, *Am. J. M. Sc.* **159** 503 (April) 1920, *New York M. J.* **112** 23 (July 3) 1920, *ibid.* **112** 56 (July 10) 1920, *abstr. J. A. M. A.* **75** 1449 (Nov 20) 1920, *ibid.* **75** 1803 (Dec 25) 1920, *Am. J. M. Sc.* **160** 575 (Oct.) 1920, *M. Clin. N. Am.* **4** 1153 (Jan.) 1921, *Am. J. M. Sc.* **163** 60 (Jan.) 1922, and **163** 223 (Feb.) 1922, *Non-Surgical Drainage of the Gall Tract*, Philadelphia, Lea & Febiger, 1923

2 Rous, P., and McMaster, P. D. *J. Exper. Med.* **34** 47 (July) 1921

this fraction is actually more concentrated than the "C" (liver) fraction of bile. For purposes of experiment, we selected one of the biliary constituents, and measured its degree of concentration in the various fractions of bile. The element chosen was cholesterol, because its percentage can be rather easily and accurately computed. If the "B" bile comes from the gallbladder, then it should contain a greater amount of cholesterol than either the common duct bile or the liver bile (so-called).

In carrying out the experiment, the technic of Lyon was closely followed. The bile fractions were segregated as accurately as possible, the tube was connected to a fresh bottle just as soon as a color change occurred. Determining the cholesterol content of the "A" fraction was soon abandoned. This fraction always contains an unknown amount of the stimulating solution, which renders a cholesterol percentage

TABLE 1—*Cases of Average Characteristic Color Change "B" Fraction of Normal Color*

Num ber	Date	Diagnosis	"B" Fraction Cholesterol Content in Mg per 100 Cc of Bile	"C" Fraction Cholesterol Content in Mg per 100 Cc of Bile	Ratio of Choles terol Content of "B" is Compared with "C" Bile
1	5/11/22	Cholecystitis, chronic, "B" fraction slightly darker than normal	500	126	4 0 10
2	2/23/22	Cholecystitis, chronic mild	76	20	3 8 10
3	2/23/22	Normal gall tract	82	17	4 8 10
4	3/15/22	Normal gall tract	100	25	4 0 10
5	3/13/22	Cholecystitis, "B" and "C" bile slightly darker than normal	375	85	4 4 10
6	2/21/22	Cholecystitis, chronic	227	45	5 0 10
7	3/ 3/22	Normal gall tract	78	25	3 1 10
8	4/ 5/22	Normal gall tract	45	37	1 3 10
9	4/ 5/22	Normal gall tract	35	25	1 4 10
10	3/25/22	Chronic cholecystitis, mild	97	35	2 8 10
Group average			161	44	3 6 10

unreliable. The comparison, paramount in value, is that between the "B" and the "C" fractions. This procedure was carried out on twenty patients. They have been classified into three groups (Tables 1, 2 and 3). The classification was based on the intensity of color of the "B" fraction as compared with the "C" fraction, and on the character of the color change from "B" to "C" bile.

#### RATIO OF CONCENTRATION BETWEEN GALLBLADDER AND LIVER BILE

Table 1 includes a group of ten patients, whose bile when drained underwent an average characteristic color change from light lemon yellow to dark amber brown and back to yellow. Half of them had no demonstrable gall tract pathologic changes. Fifty per cent of these cases were diagnosed chronic cholecystitis from the history, physical examination and the microscopic examination of the bile. We feel that gallbladder stasis is not a constant finding in chronic cholecystitis,

although it is commonly present. The five cases of cholecystitis in this group did not have abnormal gallbladder stasis, according to this method of examination.

In each instance the "B" bile contained a greater amount of cholesterol than the "C" bile. The average amount of cholesterol in "B" fraction was 161 mg per hundred cubic centimeters of bile, the "C" fraction averaged 44 mg per hundred cubic centimeters of bile. There was an average of 3.6 times as much cholesterol in the "B" as in the "C" fraction. Rosenbloom<sup>3</sup> estimated the quantity of cholesterol in biliary fistula bile to be 261 parts per 1,000, and Hammarsten<sup>4</sup> gives 99 parts per 1,000 as the quantity of cholesterol in bladder bile. Bile taken directly from the gallbladder was 3.8 times more concentrated in cholesterol than bile taken directly from the liver. Our ratio of concentration between "B" and "C" bile, as obtained by Lyon's method, is almost identical with the ratio computed from bile withdrawn directly from the gallbladder and liver. The inference may be made that the "B" fraction, as obtained by the foregoing method, does come in large part from the gallbladder. The smaller quantity of cholesterol obtained by us as compared with the amount recovered directly from the organs in question may be explained by dilution. It would seem that both fractions are equally diluted by pancreatic and intestinal juices. Cases 8 and 9 (Table 1) have concentration ratios considerably below the others in this group, although their color changes were almost as marked as the other members of the group. This discrepancy might be accounted for by an unusual dilution of the "B" fractions by magnesium sulphate solution.

#### CONCENTRATION RATIO AS AN INDEX OF GALLBLADDER STASIS

Six cases are grouped together in Table 2 because there was a greater difference in color between the two fractions under discussion, and the "B" bile was darker than normal. The color of the "B" fraction varied between dark brown and mahogany brown or black. The average cholesterol content of the "B" bile in this group was 292 mg per hundred cubic centimeters of bile, that for the "C" bile was 36 mg per hundred cubic centimeters of bile, making the ratio of concentration between the "B" and "C" fractions 8:1. The degree of concentration of the "B" fraction was twice that of the cases in Table 1. Although this is a comparatively small series, it seems likely that an estimation of the cholesterol content of the "B" and "C" fractions will be of value in the diagnosis of gallbladder stasis. It will serve as a measure of the gallbladder's concentrating activity or an index of bile inspissation.

<sup>3</sup> Rosenbloom *J Biol Chem* **14** 241, 1913

<sup>4</sup> Hammarsten *Pincussohn's Med-Chem Lab Hilfsbuch*, Leipzig, 1912, p 388

in the gallbladder. At least it should be a much more accurate gage of that function than a comparison of colors. As the ratio of concentration gets appreciably above 4:1, gallbladder stasis should be suspected, as the ratio approaches 8:1, gallbladder stasis is present. That this observation is of significance is borne out by Rous and McMaster, who consider the concentrating activity of the gallbladder an important etiologic factor in the formation of stones. Intermittent biliary stasis, according to these investigators, is the principal predisposing cause of stones, as it gives an opportunity for excessive inspissation.

The paper of Fitz and Aldrich<sup>5</sup> is interesting along this line. They say "It appears that bile may contain relatively small or large amounts of cholesterol. From our evidence it is impossible to make clinical use of the bile cholesterol findings, as they varied so markedly in all cases

TABLE 2—Color Change More Marked Than Normal "B" Fraction Darker Than Normal

Number	Date	Diagnosis	"B" Fraction Cholesterol Content in Mg per 100 Cc of Bile	"C" Fraction Cholesterol Content in Mg per 100 Cc of Bile	Ratio of Cholesterol Content of "B" as Compared with "C" Bile
			212	25	8.5:1.0
1	3/23/22	Chronic cholecystitis, stasis			
	5/11/22	Chronic cholecystitis, same patient after 6 weeks treatment	625	111	5.6:1.0
2	3/9/22	Slight jaundice (1 year), cholelithiasis (roentgen ray)	185	25	7.4:1.0
3	2/21/22	Cholecystitis, periduodenal adhesions, duodenal ulcer	235	35	6.7:1.0
4	3/3/22	Cholecystitis, chronic stasis, ichthylia gastrica	95	10	9.5:1.0
5	4/5/22	Cholecystitis, 1 year after cholecystostomy	440	25	17.6:1.0
6	2/3/22	Cholecystitis, stasis, Staphylococcus aureus confirmed	250	25	10.0:1.0
Group average			292	36	8.0:1.0

of chronic gallbladder disease. Therefore it seems reasonable to conclude that the bile cholesterol findings alone are of no clinical significance in connection with Lyon's method, although it is possible that a comparison between the blood cholesterol and the cholesterol content of liver bile may yield information of greater clinical interest." Fitz confirms the work of Peirce<sup>6</sup> and Nathan,<sup>7</sup> who found no uniform relationship between the cholesterol content of bile and disease. In a series of twenty-five cases of chronic cholecystitis without stones, Fitz and Aldrich report an average of 551 mg of cholesterol per hundred cubic centimeters of bile taken directly from the gallbladder at operation.

<sup>5</sup> Fitz, Reginald, and Aldrich, Martha. Clinical Observations on Certain Constituents of the Bile, *J A M A* **79** 2129 (Dec 23) 1922.

<sup>6</sup> Peirce, S J S. Der Gehalt der menschlichen Galle am Cholesterin und Cholesterinstern, *Deutsch Arch f klin Med* **106** 337, 1912.

<sup>7</sup> Nathan, M. Untersuchungen über den Cholesteringehalt von menschlichen Gallen, *Arch f path Anat* **228** 51, 1920.

Our average in a group of six similar cases was 292 mg per hundred cubic centimeters of "B" bile as obtained by the duodenal tube. The smaller amount of cholesterol in our series is undoubtedly due in large part to dilution with intestinal juices. Their extreme figures were 184 mg and 1,100 mg. Our extreme figures were 95 mg and 625 mg. Fitz and Aldrich drew their conclusions that the cholesterol content of bile was of no clinical significance from an examination of the gallbladder bile only. It is obvious that the cholesterol content of the gallbladder bile alone can be of no clinical importance. A substance of obscure endogenous origin and of variable exogenous origin can be of no significance as an index of disease. We do feel that a comparison between gallbladder and liver bile as obtained by Lyon's method in the manner given above will prove of definite clinical value as an index of bile inspissation in the gallbladder. Patient 6 (Table 2) was operated on. The cholesterol content of the "B" fraction before operation as obtained

TABLE 3—*Cases Having Very Little Difference in Color Between "B" and "C" Fractions*

Num- ber	Date	Diagnosis	"B" Fraction	"C" Fraction	Ratio of Choles- terol Content of "B" as Compared with "C" Bile
			Cholesterol Content in Mg per 100 Cc of Bile	Cholesterol Content in Mg per 100 Cc of Bile	
1	2/21/22	Cystic duct obstruction, biliary colic	50	75	0.7 1.0
2	2/23/22	Chronic cholecystitis, "B" bile obtained later, drainage	220	200	1.1 1.0
3	3/13/22	Cholecystitis, chronic, gallbladder atony	260	125	2.1 1.0
Group average			177	133	1.3 1.0

by the tube method was 250 mg per hundred cubic centimeters of bile. The bile removed from the gallbladder at operation contained 750 mg per hundred cubic centimeters of bile. It is possible that the difference between these two figures may represent the degree of dilution that may be expected when the bile is obtained through the tube. We do not feel that this dilution interferes with the ratio of concentration, as both fractions are undoubtedly equally diluted by the intestinal juices. The operative finding in the foregoing case was chronic cholecystitis, which confirmed our preoperative diagnosis. The bile, as obtained from the gallbladder at operation, was a very thick,ropy static bile.

#### CONCENTRATION RATIO IN CYSTIC DUCT OBSTRUCTION

Three cases in which there was very little difference in color between the "B" and "C" fractions, were grouped together in Table 3. It was not possible to make an accurate segregation of fractions, although in two of them, there was a very slight color change. The separation of fractions in Case 1 was made by time. We separated the bile which



appeared from three to thirty minutes after stimulation, determined the cholesterol content, and compared it with the cholesterol content of the bile which was drained from thirty minutes to one hour after stimulation. There was no color change in this case. At operation, a stone was found obstructing the cystic duct, accounting for the absence of a "B" fraction. The patients in Table 3 had all been drained previously. The absence of a "B" fraction of bile was not transitory.

By consulting the table, it will be noted that in each case the difference between the quantity of cholesterol in the two fractions is slight. The average cholesterol value for the so-called "B" fraction was 177 mg per hundred cubic centimeters of bile, as compared with 133 mg per hundred cubic centimeters of bile, the average cholesterol content of the "C" bile. The group concentration ratio is 1.3:1.0. As the concentration ratio decreases markedly below the normal, some interference with the evacuation of bile from the gallbladder should be suspected. The commoner things to consider are atony, atrophy, thickening, cystic duct obstruction by stone, mucus, inspissated bile or adhesions. A diagnosis of cystic duct obstruction cannot be made on the findings of one drainage. The failure to obtain a "B" fraction occurs not infrequently when a patient uses the tube for the first time, particularly if there has been considerable gagging and retching. The violent excursions of the diaphragm probably cause the bile to be mechanically evacuated from the gallbladder before the tube has entered the duodenum. We have made it a rule never to diagnose cystic duct obstruction unless there has been an absence of gallbladder bile after three drainages.

#### COMPARISON OF GROUP AVERAGES

In Table 4 the significance of the group averages may be grasped at a glance. The average amount of cholesterol in the "C" bile was practically the same for the first two groups. The third group shows a relatively high cholesterol content in the "C" fraction. It is obviously

TABLE 4—*Group Averages*

	Average Cholesterol Content of "B" Bile	Average Cholesterol Content of "C" Bile	Average Ratio Between "B" and "C" Bile
Group 1—10 cases	161	44	3.6:1.0
Group 2—6 cases	292	36	8.0:1.0
Group 3—3 cases	177	133	1.3:1.0

impossible to compare the liver bile of one group of cases with the liver bile of another series, for the same reason that the bile from various gallbladders cannot be compared with the hope of gaining information of diagnostic import. The quantity of cholesterol being excreted from the liver varies from hour to hour and from day to day. However, the

increase in the amount of cholesterol in the "C" fraction of the third group is so great that it may be of some significance. The partial cystic duct obstruction which was present may have caused the liver ducts to take on a compensatory concentrating activity, or in at least two of the cases, the gallbladder may have emptied so slowly, that an intimate mixture of the "B" and "C" bile occurred. In that event the gallbladder bile would have raised the cholesterol value of what we classified (for purpose of tabulation) as "C" bile.

#### SUMMARY

1 Nonsurgical drainage of the gall tract, following the technic of Lyon, was performed on nineteen patients. The bile was segregated as accurately as possible into three fractions, Lyon's "A," "B" and "C" bile. A cholesterol determination was made on the "B" and "C" bile in each case.

2 Ten patients having a normal color change showed an average of 3.6 times as much cholesterol in the "B" as in the "C" bile. The ratio 3.6:1.0 may be considered the normal concentration ratio between the gallbladder and liver bile as obtained by the duodenal tube method, or the inspissation index of the normal gallbladder. This is really a numerical measure of the gallbladder's concentrating activity.

3 From six cases in which the color change was more marked than normal, and in which the "B" bile was darker, a concentration ratio of 8:1 was obtained. An estimation of the cholesterol content of the "B" and "C" bile, as obtained by the duodenal tube, promises to be of value in the diagnosis of gallbladder stasis. An inspissation index of 8:1 or higher is indicative of abnormal gallbladder stasis.

4 As the ratio is appreciably decreased below 3.6:1, some interference with the normal emptying of the gallbladder should be suspected.

#### CONCLUSIONS

This experiment supports Lyon's contention, that the "B" fraction of bile, as obtained by nonsurgical drainage of the gall tract, does come in large part from the gallbladder. The cholesterol content of the "B" as compared with the "C" bile is of value in determining whether or not the gallbladder is emptying. It also serves as a fairly accurate gage of the bile concentration activity of the gallbladder, and consequently of the presence or absence of gallbladder stasis.

# THE VITAL CAPACITY OF THE LUNGS AND ITS SIGNIFICANCE IN HYPERTHYROIDISM

C A McKINLAY, M D

MINNEAPOLIS

While a growing number of reports indicate extensive study of the vital capacity of the lungs in cardiac and pulmonary disease, fewer are available in hyperthyroidism. In consideration of increased circulatory demands and cardiac stress, as well as the increased total ventilation of the lungs in hyperthyroidism, this report was thought to be justified. Frequent references to the reduction of vital capacity of the lungs in cardiac decompensation that occurs even before the physical signs of circulatory stasis have become apparent have been found. Since the work of Hutchison<sup>1</sup> it has been suggested by Siebeck<sup>2</sup> that the reduction of vital capacity is due to engorgement of pulmonary vessels with alveolar fixation, by Ulrich and Nathanson<sup>3</sup> that it may be present before signs of edema appear at the lung bases, by Burton-Optiz<sup>4</sup> that a marked decrease in vital capacity actually signifies cardiac decompensation, and by McClure and Peabody<sup>5</sup> and by Levine<sup>6</sup> that the decrease may be present with noncongestive types of myocardial insufficiency, as shown in angina pectoris. Aside from the cardiac causes of diminished vital capacity, those due to pulmonary and pleural disease are mentioned, but will not be directly considered in this paper. In hyperthyroidism, respiration is altered early in the course of the disease as is shown by greater minute volume of pulmonary ventilation associated with increased metabolism, and possibly with myocardial involvement as progression occurs.

Peabody and Wentworth<sup>7</sup> reported that of seven cases of Graves disease the vital capacity was over 80 per cent of normal in five, and between 67 and 75 per cent in two. In all, the decrease in vital capacity corresponded to the tendency to dyspnea. Recently Rabinowitch<sup>8</sup>

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\* From the Department of Medicine, University of Minnesota.

1 Hutchison, J. *Med Clin Fr London* **29** 139, 1846.

2 Siebeck, R. *Deutsch Arch f klin Med* **100** 204, 1910.

3 Ulrich, H. L., and Nathanson, M. H. *Minnesota Med* **4** 721 (Dec) 1921.

4 Burton-Optiz, Russell. *The Vital Capacity of "Cardiacs," J A M A* **78** 1686 (June 3) 1922.

5 McClure, C. W., and Peabody, F. W. *Relation of Vital Capacity of Lungs to Clinical Condition of Patients with Heart Disease, J A M A* **69** 1954 (Dec 8) 1917.

6 Levine, S. A. *Angina Pectoris, J A M A* **79** 928 (Sept 16) 1923.

7 Peabody, F. W., and Wentworth, J. A. *Clinical Studies on the Respiration, Arch Int Med* **20** 468 (Sept) 1917.

8 Rabinowitch, I. M. *The Vital Capacity in Hyperthyroidism with a Study of the Influence of Posture, Arch Int Med* **31** 910 (June) 1923.

reported a study of the vital capacity of sixty patients with Graves disease and found reduction parallel to the severity of the disease as measured by the basal metabolism

Peabody<sup>9</sup> and co-workers have studied, in twelve young men, the maximum minute volume of pulmonary ventilation following exercise, and found it to be a factor of the vital capacity, which may be taken as its index. They call attention to the fact that the minute volume has a close relationship to the fundamental processes of metabolism, indicating a broader physiologic significance than the vital capacity determination alone. It had also been observed by Peabody and Wentworth<sup>10</sup> that the minute volume of pulmonary ventilation at rest and the vital capacity of the lungs have no relationship, except that in patients with the vital capacity below 60 per cent of normal, the minute volume was quite constantly increased.

The pulse rate, on account of its acceleration and the increased circulatory demand in exophthalmic goiter, has been studied in relation to the minute volume of pulmonary ventilation, vital capacity of the lungs and basal metabolism. Clinical estimation of the severity of the disease has been made, especially with reference to cardiac signs and to evidence of myocardial insufficiency. No cardiac functional tests were done. Hence, in the absence of signs of decompensation or râles at the lung bases, and, in many patients, of demonstrable cardiac hypertrophy, symptoms including dyspnea, palpitation, and rapid heart have been interpreted as indicative of cardiac embarrassment. It should be mentioned that the patients with marked cardiac symptoms often had, in addition, evidence of nervous system involvement including psychic and emotional changes.

The patients were seen either in dispensary or hospital service. The duration of illness was possibly longer than in patients seen in private practice. No conscious selection of cases was made. It was thought not justifiable, however, to obtain data from a few severely toxic patients who came under observation during the period so they were omitted. There were thirteen males and forty-four females whose age limits varied from 11 to 59 years. In forty-eight, the diagnosis was exophthalmic goiter and in nine toxic adenoma.

Eight deaths occurred in the cases presented. One of these was due to collapse of the trachea and was not associated with thyroid toxemia. Of the seven so associated, three died within twenty-four hours after surgical treatment, one thirteen days thereafter and three before its institution. Clinical evidence pointed to severe toxicity in four of these patients, in three, the prognosis had been considered good.

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9 Sturgis, C. C., Peabody, F. W., Hall, F. C., and Fremont-Smith, F. Clinical Studies on the Respiration, *Arch. Int. Med.* **29**: 236 (Feb.) 1922.

10 Peabody, F. W., and Wentworth, J. A. *Ibid.*

TABLE 1—*Material Studied*

Case No.	Name	Sex*	Age	Pulse Rate	Vital Capacity, per Cent of Normal	Basal Metabolic Rate, per Cent Plus	Minute Volume of Pulmonary Ventilation, Liters	Minute Volume Divided by Surface Area	Cardiac Symptoms
1	W O	♂	24	86	100	33	8.3	4.5	None recorded
2	F I	♀	28	96	82	35	9.3	5.85	Palpitation
3	J W	♂	21	98	107	11	11.0	5.7	Palpitation, weakness
4	S H	♂	21	114	106	49	9.08	1.91	Weakness, palpitation
5	I W	♀	45	85	101	19	8.6	5.11	Palpitation, death due to collapse of trachea
6	E S	♀	28	88	74	25	8.11	6.23	Weakness, palpitation
7	L L	♀	22	110	82	37	7.7	5.51	Palpitation, weakness
8	H P	♂	19	120	79	27	9.1	5.29	Dyspnea, tachycardia
9	A K	♀	15	120	74	36	7.7	4.81	Palpitation, weakness
10	A S	♀	18	134	54	84	7.89	5.76	Dyspnea, palpitation, weakness, died
11	K K	♀	39	160	52	74	10.25	5.60	Dyspnea, palpitation, cardiac hypertrophy
12	C A	♀	32	148	66	43	6.9	1.6	Dyspnea, weakness, cardiac hypertrophy, died
13	M R	♀	20	122	63	23	6.4	3.53	Weakness, palpitation
14	L G	♀	22	104	76	30	5.09	2.29	Palpitation, weakness
15	L K	♀	22	98	67	28	6.42	3.78	Syncope, palpitation, weakness
16	H B†	♀	42	88	76	32	6.89	3.96	Not obtained
17	K N†	♀	59	91	73	20	5.44	3.31	Dyspnea, weakness
18	L H	♀	19	98	92	37	7.61	1.25	
19	L A	♀	25	83	67	19	5.11	3.43	Dyspnea, weakness
20	C L	♀	17	118	70	15	6.15	4.3	Pneumothorax, no cardiac symptoms
21	J J	♂	36	101	85	31	7.61	1.37	Palpitation
22	C R	♀	22	158	63	63	7.17	1.98	Dyspnea, palpitation, weakness, death 13 days after operation
23	E L	♀	24	127	61	69	7.77	5.29	Palpitation, precordial pain, weakness
24	M K	♀	27	130	66	56	8.63	4.96	Cardiac hypertrophy, dyspnea, death following operation
25	L M	♀	20	104	92	53	9.01	5.03	
26	A W	♀	11	120	67	32	9.59	8.56	Palpitation
27	F S	♀	19	92	92	35	8.83	5.51	Weakness
28	M C†	♀	18	92	82	23	5.3	3.48	Weakness
29	L M	♀	40	121	74	43	6.16	3.97	Palpitation, dyspnea
30	F B	♀	15	120	58	36	6.70	5.19	Palpitation, dyspnea
31	F S	♀	19	103	75	31	7.85	4.3	Weakness, palpitation
32	A W	♀	45	80	77	27	5.71	3.71	Dyspnea
33	G B	♀	17	96	85	21	5.11	3.5	Weakness
34	H A	♀	33	100	69	37	5.99	4.00	Dyspnea, weakness
35	G C	♀	26	97	60	24	7.42	3.63	
36	R L	♀	32	80	71	23	5.90	3.35	Weakness, palpitation
37	D H	♀	29	140	58	39	6.29	1.33	Palpitation, dyspnea, death, postmortem, no cardiac hypertrophy
38	S B†	♀	51	96	66	27	6.75	3.88	Dyspnea, cough, palpitation
39	G W†	♀	55	93	63	29	6.67	1.73	Weakness, dyspnea, previous edema of ankles, roentgen ray, heart normal outline
40	I L	♀	27	137	62	29	5.78	3.61	Slight dyspnea, palpitation, fatigue
41	A K	♂	16	135	58	87	8.81	5.68	Dyspnea, palpitation, weakness, death following operation
42	O P†	♀	49	84	60	28	6.18	3.91	Palpitation
43	B A	♂	20	100	88	18	5.14	3.23	Weakness
44	J B	♂	36	100	89	28	7.20	5.14	Weakness, palpitation, tachycardia
45	J A	♀	31	134	77	61	7.34	5.16	Palpitation
46	M F†	♀	45	149	43	82	9.09	5.61	Dyspnea, weakness, palpitation, has had edema
47	I D†	♀	36	86	86	35	8.4	5.38	Palpitation, weakness
48	O H	♂	42	116	91	32	7.73	4.22	Dyspnea, palpitation, weakness

TABLE 1—*Material Studied—(Continued)*

Case No	Name	Sex*	Age	Pulse Rate	Vital Capacity, per Cent of Normal	Basal Metabolic Rate, per Cent Plus	Minute Volume of Pulmonary Ventilation, Liters	Minute Volume Divided by Surface Area	Cardiac Symptoms
49	F E	♀	32	90	52	32	5.76	4.00	Weakness, possible complicating factor of old fibroid tuberculosis
50	L A	♀	19	116	65	52	8.63	5.04	Dyspnea, weakness
51	A S	♀	24	116	75	49	7.7	5.27	
52	L T	♀	35	102	53	36	7.82	4.59	Dyspnea, weakness, swelling of ankles
53	O C	♀	25	102	104	47	6.54	4.09	Weakness
54	E B	♀	23	105	67	24	7.54	4.09	Dyspnea, weakness
55	W F	♀	32	98	110	22	5.13	3.39	Palpitation only
56	A O†	♀	55	111	78	78	8.6	5.88	Palpitation, precordial pain, normal ejection outline
57	I S	♀	23	112	57	59	7.52	4.82	Dyspnea, palpitation, precordial pain death following operation

\* In this column, ♂ indicates male ♀, female

† Diagnosis was toxic adenoma in cases marked with dagger, in all others, exophthalmic goiter

## METHODS

The basal metabolism was obtained by the Tissot method with the use of the Haldane apparatus. The values for the minute volume of pulmonary ventilation were taken from the same records. These values were arbitrarily divided by the surface area obtained by DuBois and DuBois<sup>11</sup> height and weight chart. It was thought that values relatively more accurate could thus be obtained than is possible without consideration of height and weight. The patients were prepared in the usual manner in the postabsorptive stage, from twelve to fourteen hours after any food intake, and after a twenty minute rest period. The pulse rates were taken after at least twenty minutes of rest. The vital capacity readings were usually obtained with the patient standing and the highest

TABLE 2—*Control Series*

85	84	77	89	98	80
101	87	87	85	90	115
82	82	77	82	87	77
105	91	104	117	85	85
125	83	116	92	83	82
92	82	84	89	102	87
109	75	90	88	81	109
76	85	82	98	106	107

of three attempts was recorded. The standards used were those of West,<sup>12</sup> and the application made by the simplified method of Myers.<sup>13</sup> A control series (Table 2) of forty-eight cases with colloid goiter was

11 DuBois, D., and DuBois, E. F. A Formula to Estimate the Approximate Surface Area if Height and Weight be Known, *Arch Int Med* **17** 863 (June) 1916

12 West, H. F. Clinical Studies on the Respiration, *Arch Int Med* **25** 306 (March) 1920

13 Myers, J. A. *Am Rev Tuberc* **7** 161 (May) 1923

included to show the vital capacity values obtained under similar technic. This series gave an average of 90 per cent of the normal with 75 per cent as the lowest single variation.

This table represents forty-eight cases of colloid goiter, 6 males and 42 females, chiefly young adults. The values represent vital capacity per cent of normal. The numerical average was 90 per cent, with the low extreme of 75 per cent.

In Chart 1 it is seen that in women the vital capacity has a tendency to fall with increase in the basal metabolic rate, although there is wide variation in the vital capacity of individual cases.

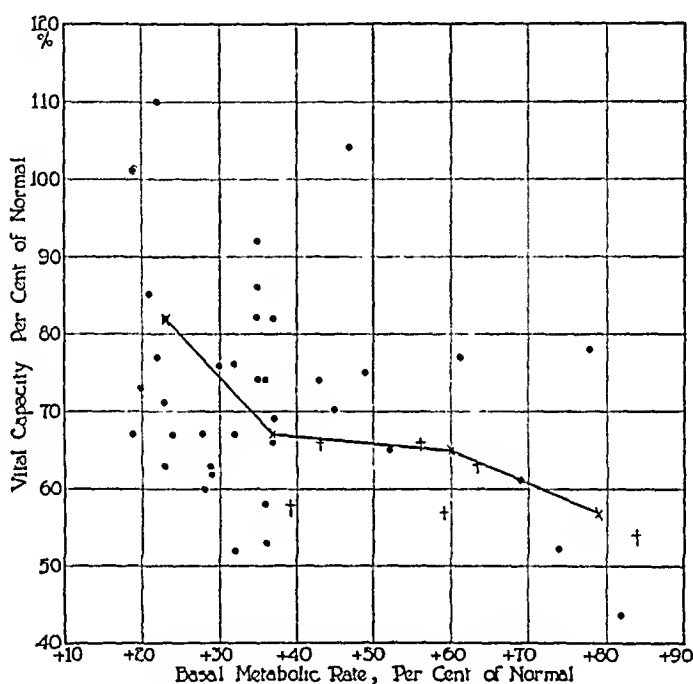


Chart 1—The greater average reduction of the vital capacity in women, with increase of basal metabolic rate, also grouping of fatal cases. Fatal cases marked with †. Death due to collapse of trachea in case marked •.

In Chart 2, which includes men and women, an increase is found in the line of averages between the metabolism rates of 40 and 50 per cent. This increase is interpreted as due to the incidence in a small group of young men with hyperthyroidism of short duration, which was well tolerated clinically and in whom the vital capacity was normal. Less often was the vital capacity normal in women in the same series, and less often were women able to carry on work without marked fatigue and dyspnea. The patients with signs of severe toxemia all showed marked reduction of the vital capacity. Its reduction in all fatal cases of thyroid toxemia amounted to not more than 66 per cent of the average normal standards. Of the total number of cases with the vital capacity of 66 per cent below the standards used, the mortality

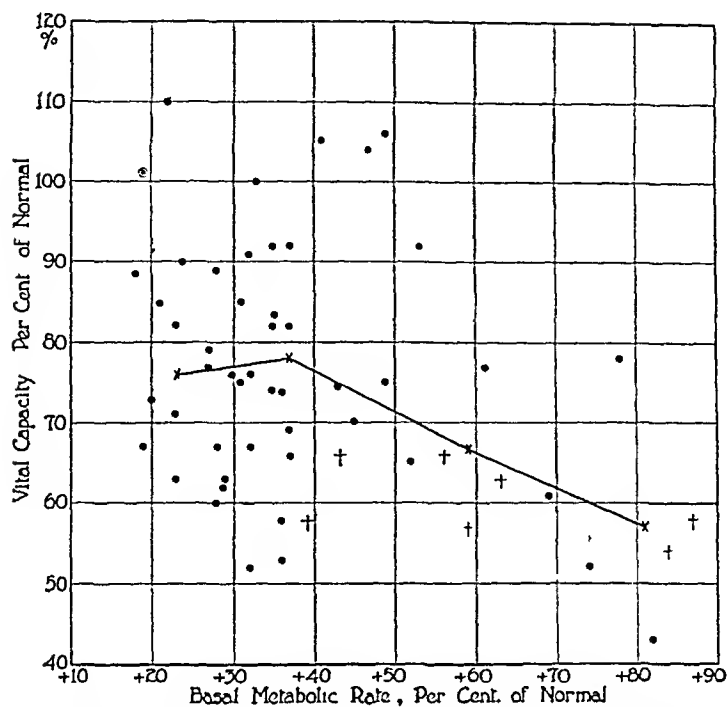


Chart 2—Same factors as Chart 1, with both men and women

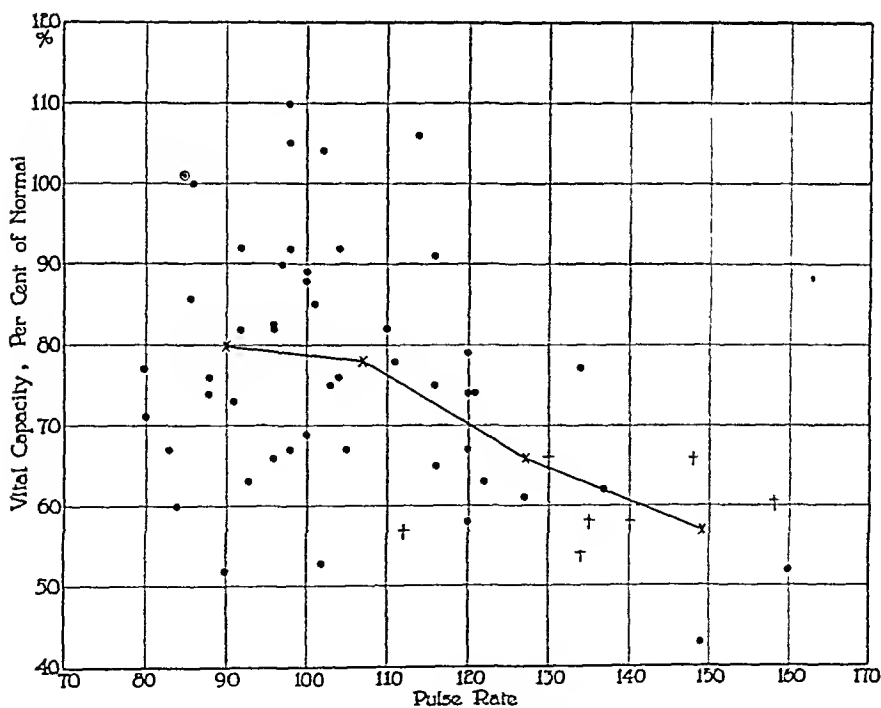


Chart 3—The greater average reduction in the vital capacity, with increase of pulse rate, also grouping of fatal cases



rate was about 33 per cent. It will be noted also that all patients with the basal metabolism above 66 per cent of the average normal capacity showed reduction of the vital capacity below 70 per cent of normal. Of patients whose vital capacity was below 70 per cent of normal, a much greater proportion showed marked signs of cardiac insufficiency and demonstrable hypertrophy. Dyspnea was more marked, tachycardia increased.

More constant is the relationship between increased pulse rate and decreased vital capacity as is shown in Chart 3. Averages show that with increasing pulse rates the vital capacity diminishes. The fatal cases are all grouped together. All show pulse rates of 112 and above, with the vital capacity reduction as before mentioned.

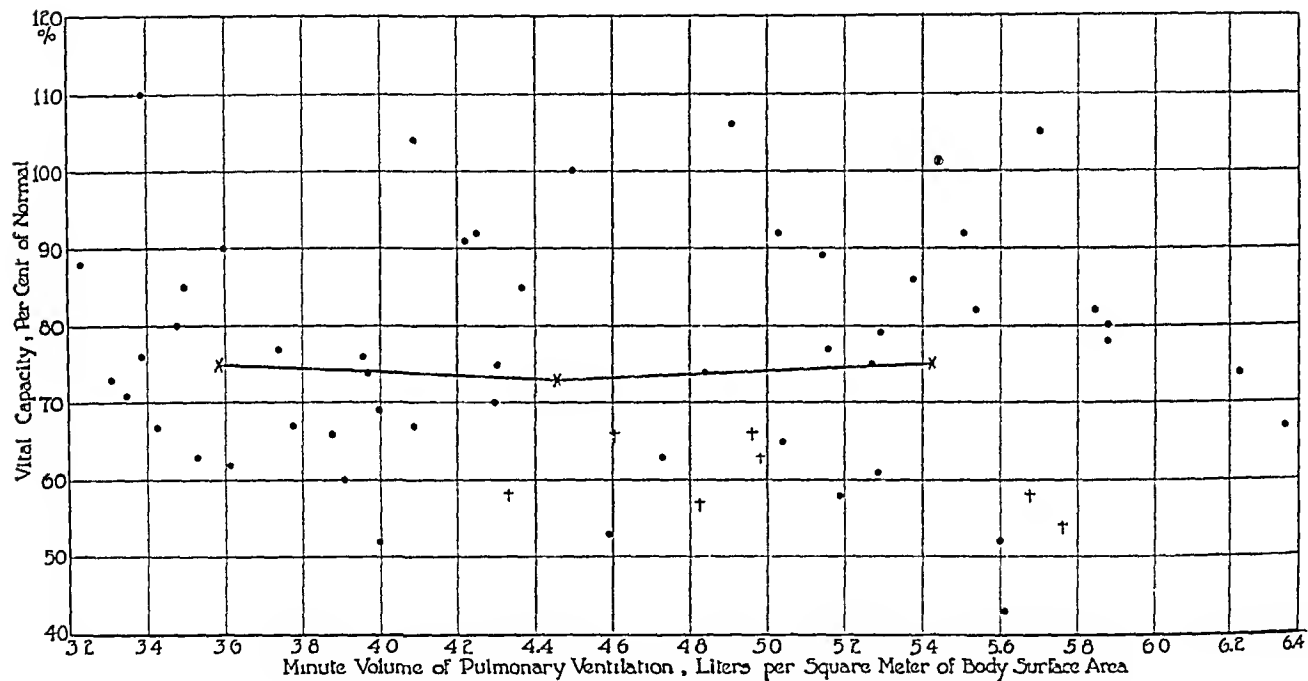


Chart 4—The absence of correlation between the vital capacity, and the minute volume of pulmonary ventilation per square meter of body surface area at rest.

No correlation is seen between the vital capacity and the minute volume, although it is to be noted in Chart 4 that there were no patients with a vital capacity below 60 per cent of normal in whom the minute volume fell below 4 liters per square meter of body surface. There were, however, sixteen patients with the minute volume of less than 4 liters per square meter of body surface area and vital capacity above 60 per cent of average normal standard.

#### COMMENT

In the absence, chiefly, of diseases of the lungs and pleura, reduction of the vital capacity of the lungs had generally been considered to

indicate cardiac decompensation. In none of the patients studied were found either physical signs of congestion at the lung bases or edema of the subcutaneous tissues. Early in circulatory stasis such signs may not be present at a time when the vital capacity is definitely reduced. The vital capacity reductions have been interpreted as indicative of cardiac decompensation or subcompensation, and have pointed thereto more surely than physical examination alone. The same value of vital capacity determinations obtains in cardiac involvement associated with exophthalmic goiter, as in that due to other causes. The prominence of tachycardia, cardiac hypertrophy, and dyspnea, associated with reduced vital capacity in the fatal cases, has indicated that cardiac failure has played an important part in causation of death.

It seems to be worthy of stressing that all patients with high basal metabolic rates, with one exception, showed very definite reduction of the vital capacity. On the other hand, in patients with lower rates, death occurred only in those whose vital capacity was below 70 per cent of normal. In the patients studied, prognosis would appear to depend not so much on the degree of increase of the basal metabolism above 30 per cent as on the reduction of the vital capacity below 70 per cent of normal. The vital capacity reduction has therefore distinct prognostic value.

The lack of any definite correlation between the minute volume of pulmonary ventilation at rest and the vital capacity of the lungs is worthy of note, in view of the determination that the maximum minute volume is a factor of the vital capacity in healthy young men. The observation of Peabody and Wentworth that in cardiac decompensation when the vital capacity fell below 60 per cent of normal the minute volume was always increased, held true also in the patients in this series with hyperthyroidism.

The reduction in vital capacity in the cases studied appears to be due to cardiovascular insufficiency. It seems reasonable to consider that decreased vital capacity and increased pulse rate are partly of myocardial origin. This is indicated by the preponderance of cardiac signs and symptoms in the patients with marked diminution of the vital capacity. Such explanation is in keeping with the clinical experience of numerous observers. That a lower vital capacity may be an important factor in the production of dyspnea in hyperthyroidism, as suggested by Rabinowitch, seems unreasonable except in the possible instance of hyperthyroidism coexistent with extensive pathologic change of the lungs, sufficient in itself to cause a marked reduction. Careful study will probably reveal that in the great majority of cases the dyspnea and vital capacity reduction are proportional to the reduction of the functional capacity of the heart.

No special comment appears to be necessary concerning the correlation of increase of pulse rate and basal metabolism, of pulse rate and minute volume, and of the minute volume and basal metabolism. Such correlation is evidence, in part, of increased circulatory demand and increased pulmonary ventilation associated with the supply of larger amounts of oxygen to the body and removal of carbon dioxide therefrom, when the heat production is increased.

#### CONCLUSIONS

1. Marked reduction of the vital capacity of the lungs below 70 per cent occurred in a great majority of severely toxic cases of hyperthyroidism.

2. In the patients studied, reduced vital capacity of the lungs pointed more definitely to bad prognosis than did the degree of increase of the basal metabolism.

3. The minute volume of pulmonary ventilation at rest was not a factor of the vital capacity.

# THE NASAL ACCESSORY SINUSES IN CARDIOPATHIES <sup>1</sup>

## PRELIMINARY REPORT

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Through the courtesy of the chief of the otologic service, Dr Samuel J Kopetzky, I was enabled to examine the nasal chambers and accessory sinuses in a great number of cadavers. While some of the findings were very interesting, as they were not recognized before death, others were extremely important because they had a direct or indirect relation to the disease of the patient.

Most of us recognize the significance of, and take for granted the relation of focal infection to a great many general affections of the body. Every day we find newly discovered foci of infections. The important ones we have in the teeth, the tonsils, the sinuses, the prostate and the appendix. Each of these may become infected and produce toxins that may be carried through the blood to other parts or organs of the body. And as a result, we have the various forms of rheumatism, some varieties of heart disease, a number of the arthritides, several forms of kidney disease, peculiar affections of the eye, chorea infantum and a good many other infections. More and more we are beginning to realize that an abscess cavity, although walled off and circumscribed, yields to the system toxic substances through the very walls enclosing it, via the capillaries and lymph channels.

These focal infections are sometimes overlooked, either through carelessness or accident. Especially is this so when a patient is brought to us acutely ill, with stormy symptoms, such as is observed in acute vegetative endocarditis. We are then so concerned with the pulse and temperature, the blood pressure, the blood culture and the electrocardiograms, that we quite forget to study the condition which may perhaps be the etiologic factor in the case, as, for example, the accessory nasal sinuses.

Recently, arrangements have been made at the hospital that every new case should be thoroughly and completely examined by a trained ear, nose and throat specialist. In this manner very interesting facts have been brought to light. Children sent in to the hospital with a tentative diagnosis of "pneumonia" had their ear drums incised, and they recovered from an acute attack of otitis media. In other patients

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\* From the Otolaryngological Department of the Beth Israel Hospital.

<sup>1</sup> Read before the Beth Israel Hospital Alumni Association, March 27, 1924.

we found nasal pathologic changes suggestive of sinus disease, such as polypi, discharge, crust formation and a parched and glossy rhinopharynx. Advice was offered and proper care given to those patients, whether or not the findings had any relation to the disease in question. Furthermore, at necropsy, many cases were examined from the medical services of the hospital, and results recorded.

Of the many cases I have examined two were very interesting.

#### REPORT OF CASES

CASE 1—A young woman was admitted to the hospital on May 9, 1922, with a diagnosis of chronic cardiovalvular disease. In the history, no complaint was made about the nose and throat in the present or in the past. The patient's most important subjective symptoms were pain in both feet for the duration of one year. Precordial pain for the duration of seven weeks. Pain in the back, lasting for four days. Pain in both hands for one day.

In the physical examination we found the following: Ears. There was no mastoid tenderness or discharge. Nose. There was no nasal discharge or obstruction. Teeth. Were in good condition with few missing. The pharynx was congested and the tonsils were not visible.

The patient entered the hospital with a temperature of 100.6, which reached the highest point of 102.6 on the second and third day, then it gradually came down but only reached normal on May 20, 21, 22, 24 and 31. Her pulse on admission was 124 (the most frequent) and varied between 80 and 112. She was discharged from the hospital on June 7, four weeks after admission, with a temperature of 99 and a pulse 104.

From the foregoing one can readily see that the accessory sinuses having been reported negative, no roentgenogram was taken of them, she was discharged from the hospital apparently improved.

The patient was then sent to the country for three weeks and returned in a much worse condition than when she left. The condition became progressively worse, and on November 1, she was readmitted to the hospital.

Her chief complaint now was dyspnea and cough. The temperature was 105 and pulse 134. A diagnosis of lobar pneumonia, acute endocarditis and chronic cardiovalvular disease was made.

In the physical examination we found the following: Head. Bony structure and scalp normal. Accessory sinuses normal. Ears and nose normal. Teeth well taken care of and in fair condition. Pharynx congested, tonsils atrophied.

Again we read the accessory sinuses were declared flatly negative and consequently no roentgenogram was advised. Since no pathologic change was seen by the examiner it was taken for granted that no infection was there.

A blood culture was taken and reported sterile. The course of illness was stormy and the patient died, November 7, on the seventh day of her stay in the hospital.

A necropsy was done the same day. While the house staff were examining the abdominal and thoracic organs, I proceeded to investigate the nasal chambers and accessory sinuses. My findings were as follows: Nasal chambers narrow, middle turbinates swollen, and between these and the lateral nasal walls strings of thick greenish pus were present. The septum was in the median line. Both maxillary sinuses were then opened through the canine fossae, and I was astonished to find both chambers filled with thick greenish pus resembling cream cheese. The mucous membrane lining the sinuses was found degenerated and the overlying bone abnormally thick and brittle. The mucous membrane was in parts dark green, the characteristic color of gangrene. The odor was very offensive. The ethmoidal labyrinth showed a hyperplastic ethmoiditis and the sphenoid and frontal sinuses were empty.

Analyzing the foregoing findings one may justly assume that the patient had a double purulent maxillary sinusitis for many years. Furthermore, we may claim that the involvement of both maxillary sinuses gave rise directly or indirectly to the cardiovalvular disease.

It may be of academic interest to give here the report of the pathologic laboratory. Anatomic diagnosis: Acute vegetative endocarditis, chronic congestion of the lungs, chronic congestion of liver, spleen and kidneys. Microscopically, no bacteria were found.

CASE 2—A man aged 49, was admitted to the hospital on April 4, 1923, with a diagnosis of chronic valvular disease complicated by chronic parenchymatous nephritis. His principal complaint on admission was dyspnea of five weeks duration, weakness, cough and hemoptysis.

There was nothing in the history that would suggest intranasal or sinus pathologic change. The physical examination likewise coincided with the history and read as follows: Head: no abnormalities, ocular movements normal, no nystagmus. Pupils equal, regular, and react to light and in accommodation. Ears and nose normal to external examination. Teeth in bad condition, breath foul, tongue dry and coated, tonsils cryptic and pharynx congested. The rest of the examination was not important, as it has no significance in this paper. A blood culture was taken and reported sterile.

As this patient entered the hospital following the introduction of the system whereby each incoming patient had to be examined thoroughly by a trained nose and throat specialist, it fell to Dr. A. A. Schwartz to examine this patient. His findings are recorded as follows: Atrophic rhinitis, large crusts in left nares and pus in both nares. Pus on pressure over right tonsil. Tonsils enlarged and submerged. On pressure, ecchymosis found over anterior pillars. Vocal cords slightly reddened. No ulcerations or masses. Recommend roentgenogram of sinuses. Unfortunately, this good advice was never heeded.

The patient died, April 21, seventeen days after admission. Permission was obtained for necropsy, which was performed the same day.

Necropsy findings: Nasal chambers roomy, mucous membrane covered here and there with crusts. Slight amount of purulent discharge on the floor of right nasal chamber. Turbinates normal in size, septum straight. A small polypus was present between middle turbinate and lateral nasal wall on right side. On opening the right maxillary sinus through the canine fossa I found the cavity half full of pus. On removing it, the mucous membrane was found flabby, degenerated, and studded with polypi. These were especially numerous at the junction between the floor and nasal wall of the antrum. The left antrum and all the other accessory sinuses were found to be negative.

Anatomic diagnosis and laboratory report: acute vegetative endocarditis, chronic congestion of lungs, chronic congestion of liver, spleen and kidneys. Microscopic examination: no bacteria found.

Of course I would not like to be misunderstood in claiming that had these sinuses been roentgenogrammed, a diagnosis made, and the pathologic changes eradicated, the patients would not have died. But at least we should have had the satisfaction of knowing that everything possible had been done and that nothing in the cases had been overlooked.

CASE 3—A young woman (age not given), entered the hospital on Aug. 28, 1923, with a history of having had rheumatic fever ten years ago. She was brought in so seriously ill that a detailed description of her subjective symptoms were impossible. Suffice it to state that, objectively, dyspnea, orthopnea, cyanosis and edema of the lower extremities were present. Her only complaint was precordial pain.

The physical examination read as follows: General appearance that of an adult woman acutely ill, deeply cyanotic, orthopneic and dyspneic. Respirations rapid, body cold and clammy. Head: Scalp normal. Eyes: No ptosis, nystagmus or strabismus. Pupils regular, round, equal and react to light and in accommodation. Ears, normal. The rest of the physical examination is not important in this paper.

The patient lost ground rapidly and died on August 30, two days after admission

At necropsy on the following day was revealed polypoid degeneration of the middle turbinate, which was covered with purulent secretion. The left maxillary sinus, opened through the canine fossa, showed the cavity filled with pus and polyp. All the other accessory sinuses were empty. As this patient was only in the hospital two days and was admitted in a dying condition, there was no time to investigate the nasal accessory sinuses by a competent nose and throat specialist. Nor was there much time to do the many other laboratory and clinical investigations. I mention this case merely to show the relation of sinus involvement to cardiac disease and the probability that this case might have had sinus empyema for a number of years, even antedating the attack of acute rheumatic fever.

### CONCLUSIONS

Having read the foregoing, one must conclude that a relation apparently exists between sinus empyema and cardiac disease, especially chronic valvular disease and subacute bacterial endocarditis. Not enough scientific work has been done on this interesting subject thus far. The bacteriology of the affected maxillary sinuses was not studied partly because the blood cultures in the before mentioned cases were sterile, and partly because I was not quite prepared for the unexpected findings. However, this important link will be the subject of a subsequent paper.

The literature on the relation of sinus disease, especially sinus empyema, to various affections of the heart is rather scanty. Having consulted a cardiologist, Dr. Morris H. Kahn, on this subject, I was advised, following a scrutiny of the literature, that almost nothing has been written on this subject. Babcock<sup>1</sup> cites three cases of myocardial involvement apparently due to abscessed teeth. In two of the cases *Streptococcus viridans* was found, following the removal of the offending teeth. In all of the three cases an autogenous vaccine was prepared and administered, the patient's cardiac involvement clearing up entirely.

Lichty<sup>2</sup> cites cases showing the relation of functional and organic disease of the heart to disease of the appendix and gallbladder. He also advises surgery and the use of vaccine.

### SUMMARY

Three cases of maxillary sinus empyema have been demonstrated postmortem, in patients dying from cardiac disease. In none of these cases has the sinus involvement been recognized before death.

A roentgen-ray examination of the sinuses is very important in all cases of cardiac disease, but especially so in chronic valvular affections and in subacute bacterial endocarditis. The nasal chambers and accessory sinuses should be thoroughly investigated by a competent nose and throat specialist.

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1 Babcock, R. H. New York M. J. (Dec. 2) 1916

2 Lichty. Ohio State M. J. 40 747-842, 1915

# BLOOD PHOSPHORUS ITS RELATION TO CANCER AND ANEMIA<sup>\*</sup>

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Moraczewski,<sup>1</sup> in 1895, demonstrated abnormally low values for the total phosphorus content of the whole blood in certain cases of cancer and these findings suggested to Groebly<sup>2</sup> and others that diagnostic significance might be attached to the phosphorus content of the blood. Groebly has reported an increased total phosphorus content of the whole blood of patients suffering from cancer, and at the same time has recognized a relationship between it and the number of red corpuscles per unit volume of blood. To show this relationship he has made use of what he terms the "phosphorus quotient" represented by the expression,  $P/R$ , where  $P$  is the total phosphorus, as phosphorus pentoxid, in 10 cc of whole blood and  $R$  is the number of millions of red corpuscles in 1 cmm of blood. Groebly considers that in normal persons the phosphorus quotient ranges from 2.64 to 2.92 and that it has a higher value, usually over 3.17 in cases of cancer. Recently, Vorschütz and Vorschütz<sup>3</sup> have published the results of an investigation in which they state that, although the total phosphorus content of the whole blood may be normal in patients with cancer, the phosphorus quotient of Groebly is uniformly high and is therefore of diagnostic importance.

The work of these authors suggested to us that determinations of the phosphorus quotient might be of great clinical value and, in the hope of confirming their work, a study was made of the blood phosphorus of persons afflicted with cancer. It was obvious from the outset, however, in view of the relationship implied in the phosphorus quotient that the persons studied as controls should include not only healthy persons, but

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<sup>\*</sup> From the Medical Service of the Collis P. Huntington Memorial Hospital. This paper is No. 16 of a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses of this investigation have been defrayed, in part, by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

1 Moraczewski, W. *Virchows Arch f path Anat* **139** 385, 1895.

2 Groebly, W. *Arch f klin Chir* **115** 261 (Feb.) 1921.

3 Vorschütz, Johannes, and Vorschütz, Jos. *Deutsch med Wchnschr* **48** 861 (June 30) 1922, *ibid*, *Arch f klin Chir* **115** 261, 1921.



also patients with anemia and polycythemia due to various causes, as well as cases of a nonmalignant nature not exhibiting anemia. Such cases as arthritis, leukemia (except one case), nephritis, etc., in which a disturbance of the phosphorus metabolism is known to occur, have been excluded from our series of cases.

In view of the current widespread interest in the inorganic phosphorus content of the blood, a determination of this also was included in the study.

#### PROCEDURE

With the methods and technic described below, determinations of the inorganic phosphorus content of the whole blood and plasma were made in twenty-one cases of cancer and forty control cases, and of the total phosphorus content of the whole blood and plasma in seventeen cases of cancer and twenty-eight control cases. The phosphorus content of the corpuscles was calculated from the determined values of phosphorus in the whole blood and plasma and the percentage by volume of corpuscles.

Blood from a vein was obtained under liquid petrolatum in the usual manner,<sup>4</sup> neutral potassium oxalate being used as an anticoagulant.<sup>5</sup> After thorough mixing, samples of blood were withdrawn from the container for determination of the total phosphorus and inorganic phosphorus content of the whole blood and the percentage by volume of corpuscles. The remainder of the blood was then centrifugalized for twenty minutes at a speed of about 1,800 revolutions to the minute, and the supernatant plasma removed for the determination of its content of total and inorganic phosphorus.

The percentage by volume of corpuscles was determined by means of an improvised hematocrit, consisting of a portion of a calibrated microburet, graduated to hundredths of a cubic centimeter. The readings in each case were made after the blood had been centrifugalized for thirty minutes at a speed of two thousand revolutions to the minute.

The total phosphorus was determined by the method of Bloor<sup>6</sup> and the inorganic phosphorus by the method of Bell and Doisy.<sup>7</sup> All values for phosphorus are expressed as milligrams of orthophosphoric acid ( $\text{H}_3\text{PO}_4$ ), per hundred cubic centimeters of whole blood, plasma or corpuscles, except that in calculating the phosphorus quotient the phosphorus is expressed as phosphorus pentoxid ( $\text{P}_2\text{O}_5$ ).

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4 As suggested by Denis and von Meysenbug the quantity of potassium oxalate was restricted to 0.1 cc. of a 20 per cent solution to each 15 cc. of blood.

5 Denis, W., and von Meysenbug, L. *J Biol Chem* **52** 1 (May) 1922.

6 Bloor, W. R. *J Biol Chem* **36** 33 (Oct) 1918.

7 Bell, R. D., and Doisy, E. A. *J Biol Chem* **49** 263, 1921.

The percentage of hemoglobin was determined by the Sahli method, with the use of a frequently standardized instrument, except in those cases in which there was a polycythemia, when the gasometric method of Van Slyke<sup>8</sup> was used. All values for hemoglobin have been reduced to the Haldane scale.

Enumerations of the blood corpuscles were made in the usual manner.

#### COMMENT

The results of the determinations are shown in the tables and charts. In the tables, the cases are arranged in order of ascending hemoglobin values.

*Inorganic Phosphorus*—Table 1 shows the results obtained in the control cases, which include normal persons and those exhibiting different degrees of anemia and polycythemia due to various causes. Table 2 shows the results obtained in twenty-one cases of cancer. In both tables nearly all the values for inorganic phosphorus in the whole blood, plasma and corpuscles are within the normal limits given by Bell and Doisy,<sup>7</sup> Briggs,<sup>9</sup> Bloor,<sup>10</sup> Tolstoi,<sup>11</sup> Tisdall and Harris<sup>12</sup> and others. Such abnormal values as do occur cannot be explained from the data at hand, but they are obviously not specific manifestations of malignant disease or of anemia or of polycythemia. These facts are illustrated graphically in Chart 1.

*Total Phosphorus*—In Tables 3 and 4, respectively, are recorded the results obtained from the determinations of total phosphorus in the whole blood, plasma and corpuscles of control cases and of those with cancer. In each instance the phosphorus quotient, calculated according to the formula of Groebly, is included.

The values for the total phosphorus content of the whole blood, plasma and corpuscles of the five normal adults are in agreement with the normal values reported by other investigators. Although markedly abnormal values, both high and low, do occur among the cancer cases and the control cases, it cannot be said that there is any definite tendency toward a specifically abnormal alteration of the phosphorus content of the blood in cancer. For the most part, it is the corpuscles that yield abnormal values for the total phosphorus content. Nucleated cells and platelets, as compared to mature red cells, are relatively rich in phosphorus, but the differences in our cases in the numbers of the former

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8 Van Slyke, D. D. *J Biol Chem* **33** 127 (Jan) 1918.

9 Briggs, A. P. *J Biol Chem* **57** 351 (Sept) 1923.

10 Bloor, W. R. *J Biol Chem* **36** 49 (Oct) 1918.

11 Tolstoi, E. *J Biol Chem* **55** 157 (Feb) 1923.

12 Tisdall, F. F., and Harris, R. I. *Calcium and Phosphorus Metabolism in Patients with Fractures*, *J A M A* **79** 884 (Sept 9) 1922.

elements in no way parallel the phosphorus content of the corpuscles. There were no cases with a white cell count of over 25,000 per cubic millimeter, nor are cases of leukemia included that have a high phosphorus content of the corpuscles due to a large number of white cells. Immature red cells (reticulocytes, etc.) contain nuclear remains which might cause them to be richer in phosphorus than adult cells. In the two cases with the greatest amount of phosphorus in the corpuscles, the reticulocytes were 30 per cent (Case 5, hemolytic jaundice) and 18 per cent (Case 7, anemia due to blood loss) while no other case showed

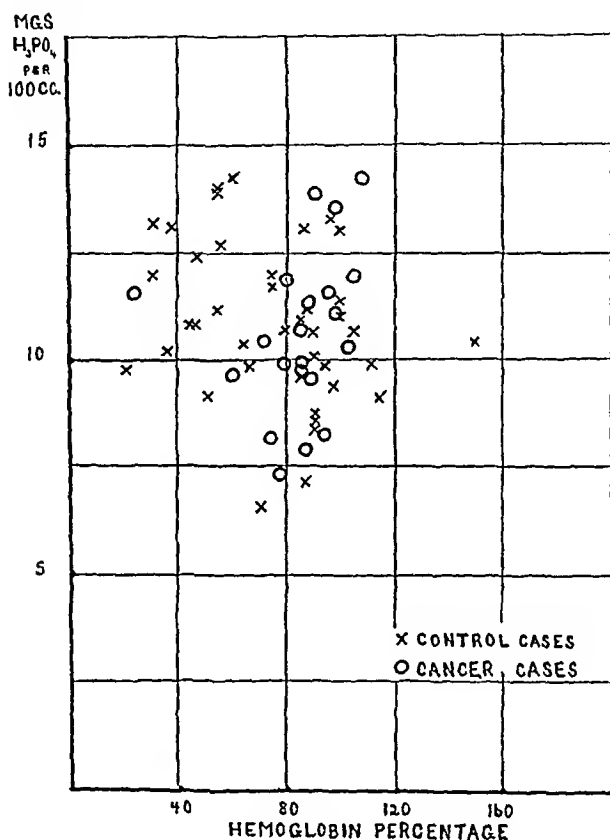


Chart 1—The lack of correlation between the inorganic phosphorus content and the hemoglobin content of the whole blood in all cases. Values for the control cases are indicated by the crosses, those for cases of cancer by circles.

so many immature red cells. Though no entirely satisfactory explanation for the abnormal values for the total phosphorus content of the corpuscles can be set forth, it is quite possible that the high values are at least partially due to an increase in the number of immature red corpuscles.

The most significant observation brought out by this study is the apparent relationship between the total phosphorus content of the whole blood and the level of the hemoglobin. This relationship is illustrated in Charts 2 and 3, in which the total phosphorus content of the whole

TABLE 1—*Inorganic Phosphorus as Orthophosphoric Acid in Blood of Control Cases*

Case No	Age	Diagnosis	H <sub>3</sub> PO <sub>4</sub> in 100 C c of			Red Blood Count in Millions	Hemo-globin, per Cent	Percent-age by Volume of Cells
			Whole Blood	Plasma	Cells			
1	58	Pernicious anemia	9.8	11.1		0.8	20	9.6
2	21	Pernicious anemia	13.1	13.2	12.0	1.4	30	12.9
3	50	Pernicious anemia	11.9	12.1	8.3	1.1	30	8.0
4	73	Pernicious anemia	10.2	10.4	9.5	1.8	35	21.3
5	65	Congenital hemolytic jaundice	13.0	10.0	28.6	2.6	37	16.8
6	20	Renal calculus, chronic blood loss	10.8	14.3		3.3	45	16.1
7	21	Duodenal ulcer, acute blood loss	12.3	11.5	16.4	2.0	45	16.9
8	19	Menorrhagia, nonmalignant	10.8	11.9	7.5	2.3	45	23.9
9	43	Renal calculus, chronic blood loss	9.2	12.1		3.3	50	22.8
10	61	Multiple myeloma	11.1	10.8	11.1	2.7	54	20.2
11	55	Pernicious anemia	12.6	13.6	6.9	1.0	55	14.8
12	51	Pernicious anemia	13.6	14.8	7.2	1.7	55	16.4
13	39	Pernicious anemia	13.5	14.0	11.9	2.8	55	29.3
14	50	Pernicious anemia	14.2	13.7	15.8	2.6	60	25.9
15	30	Chronic thrombopenic purpura	10.3	10.9	9.2	5.3	64	33.5
16	45	Erythremia (anemic phase)	9.8	10.2	9.1	3.8	66	36.0
17	46	Pernicious anemia	6.6	7.3	5.3	2.4	70	32.9
18	30	Chronic thrombopenic purpura	11.6	12.9	9.1	5.1	75	35.7
19	74	Hodgkin's disease	11.8	11.1	12.8	4.2	75	38.6
20	27	Tuberculous lymphadenitis	10.6	12.0	9.0	5.3	80	46.9
21	50	Pernicious anemia	10.8	9.0	13.7	3.0	85	38.0
22	35	Hodgkin's disease	13.0	11.7	14.7	5.7	85	46.6
23	45	Hodgkin's disease	9.6	9.5	9.7	4.3	85	34.4
24	34	Erythremia	7.1	8.0	6.5	8.7	85	57.0
25	43	Hodgkin's disease	11.2	9.6	14.3	4.7	86	33.8
26	41	Tuberculous lymphadenitis	10.0	8.3	12.9	4.5	90	36.0
27	54	Acute infectious mononucleosis	8.7	7.3	11.4	4.3	90	34.5
28	50	Chronic lymphatic leukemia	8.4	10.0	5.7	3.6	90	35.5
29	22	Tuberculous lymphadenitis	8.8	8.3	9.4		90	47.3
30	29	Normal	10.6	9.0	14.9	4.3	90	42.1
31	27	Normal	9.8	9.4	10.3	4.5	94	38.6
32	26	Normal	13.2	9.4	17.4	5.4	95	47.8
33	55	Banti's disease	9.3	10.0	8.6	4.4	95	43.0
34	47	Myocarditis	11.3	13.4	10.3	6.9	100	68.1
35	44	Erythremia	13.0	9.2	17.6	7.2	100	46.0
36	28	Normal	11.0	11.1	11.3	5.3	100	46.3
37	24	Normal	10.6	13.0	7.6	4.9	105	44.0
38	24	Normal	9.9	10.5	9.2	5.7	112	47.2
39	61	Erythremia	9.0	9.0	9.1	9.3	115	68.2
40	50	Erythremia	10.3	8.8	10.8	9.6	155	76.0

TABLE 2—*Inorganic Phosphorus as Orthophosphoric Acid in Blood of Cancer Cases*

Case No	Age	Diagnosis Carcinoma of	H <sub>3</sub> PO <sub>4</sub> in 100 C c of			Red Blood Count in Millions	Hemo-globin, per Cent	Percent-age by Volume of Cells
			Whole Blood	Plasma	Cells			
41	50	Stomach	11.5	12.7	1.9	1.8	23	11.2
42	56	Cheek	9.6	10.1	8.9		60	42.1
43	46	Cervix of uterus	10.3	6.6	18.4	4.6	72	31.1
44	44	Cervix of uterus	8.1	7.6	9.1	4.7	75	32.4
45	60	Cervix of uterus	7.3	6.7	8.8	3.6	77	26.1
46	62	Cervix of uterus	11.8	10.6	14.3	4.0	80	31.5
47	64	Jaw	9.9	9.5	10.9	4.2	80	29.8
48	33	Bladder	10.7	10.1	11.6	5.9	85	38.1
49	56	Stomach	9.7	10.4	8.2	4.3	85	31.2
50	38	Cervix of uterus	9.7	7.0	14.8	4.6	85	35.1
51	68	Rectum	7.9	7.9	7.9	5.3	87	37.1
52	37	Pancreas	11.3	8.2	15.8	4.6	89	41.3
53	65	Lip	9.5	9.7	9.1		90	40.9
54	40	Sigmoid	13.8	12.0	17.8	5.0	91	31.2
55	64	Breast	8.2	6.8	10.3	4.5	93	40.7
56	57	Breast	11.4	11.9	10.7	4.2	97	40.7
57	52	Breast and cervix of uterus	13.5	11.4	16.8	4.8	98	38.6
58	55	Prostate	11.0	9.8	12.5	4.4	99	41.7
59	55	Breast	10.2	10.5	9.8	4.6	104	39.5
60	61	Larynx	11.8	9.6	14.5	5.7	105	45.6
61	44	Breast	14.1	16.7	12.3	5.7	110	38.5

TABLE 3—Total Phosphorus as Orthophosphoric Acid in Blood of Control Cases

Case No	Age	Diagnosis	H <sub>3</sub> PO <sub>4</sub> in 100 Cc of				Red Blood Count in Millions	Hemo-globin, per Cent	Per-cent- age by Volume of Cells	Phosphorus Quotient
			Whole Blood (Actual)	Whole Blood (Theoretical)	Plasma	Cells				
2	21	Pernicious anemia	46.3	55	29.3	160.8	1.5	30	12.9	4.4
62	43	Anemia, sepsis	53.0				2.2	40	16.0	2.4
7	21	Duodenal ulcer, acute blood loss	138.8	68	38.8	629.7	2.0	45	16.9	10.0
6	20	Renal calculus, chronic blood loss	79.9	70	24.3	365.6	3.3	45	16.1	3.5
10a	61	Multiple myeloma	77.2	72	26.2	438.0	1.8	46	12.3	6.2
5	65	Congenital hemolytic jaundice	113.1	75	19.6	560.0	2.5	48	17.3	6.5
9	43	Renal calculus, chronic blood loss	54.4	75	24.8	155.7	3.3	50	22.7	2.4
10	61	Multiple myeloma	95.4	78	31.4	348.8	2.7	54	20.2	5.1
8	19	Menorrhagia, nonmalignant	89.5	78	36.2	259.4	3.8	55	23.9	3.4
13	39	Pernicious anemia	60.9	78	22.0	153.7	2.8	55	29.4	3.1
14	50	Pernicious anemia	67.6	83	34.8	161.3	2.6	60	25.9	3.7
63	62	Pernicious anemia	83.6	83	20.0	288.0	2.0	60	23.7	6.0
15	30	Chronic thrombopenic purpura	76.8	88	22.4	185.4	5.3	64	33.5	2.1
64	50	Pernicious anemia	101.1	89	30.6	249.4	2.0	65	32.9	7.3
16	45	Erythremia (anemic phase)	83.0	89	27.9	181.1	3.6	66	36.7	3.1
19	74	Hodgkin's disease	80.8	96	20.9	121.5	4.2	75	38.5	2.8
24	34	Erythremia	158.5	107	32.9	253.1	8.7	85	57.0	2.6
25	43	Hodgkin's disease	159.2	107	27.9	348.5	4.7	86	40.9	4.8
65	54	Hodgkin's disease	109.5	110	37.0	206.7	3.9	90	43.7	4.1
30	29	Normal	99.9	110	39.3	162.2	4.3	90	42.1	3.0
31	27	Normal	107.8	116	34.5	224.2	4.5	94	38.5	3.5
32	26	Normal	120.1	117	28.4	220.0	5.4	95	47.8	3.2
36	28	Normal	145.0	120	25.3	284.0	5.3	100	46.3	3.9
34	47	Myocarditis	88.4	120	13.4	123.4	6.9	100	68.2	1.8
35	44	Erythremia	112.8	120	42.4	197.3	7.2	100	45.5	2.3
37	24	Normal	133.0	123	20.8	275.6	4.9	105	44.0	4.0
39	61	Erythremia	102.1	155			9.1	138	68.5	1.6
40	50	Erythremia	160.4	169	28.5	202.1	9.6	155	76.0	2.3

TABLE 4—Total Phosphorus as Orthophosphoric Acid in Blood of Cancer Cases

Case No	Age	Diagnosis	H <sub>3</sub> PO <sub>4</sub> in 100 Cc of				Red Blood Count in Millions	Hemo-globin, per Cent	Per-cent- age by Volume of Cells	Phosphorus Quotient
			Whole Blood (Actual)	Whole Blood (Theoretical)	Plasma	Cells				
41	50	Stomach	27.2	51	16.0	115.8	1.8	23	11.2	2.1
66		Stomach	60.0				2.6	35	20.0	2.3
67		Cervix of uterus	91.8	65	44.6	241.4	2.8	39	24.0	4.7
41b	50	Stomach	91.2	78	22.2	311.0	4.3	54	23.9	3.0
68	38	Breast and fibroid uterus	110.0	81	21.4	340.0	4.7	56	27.8	3.5
52	37	Pancreas	101.1	87	35.3		3.2	63		4.5
69	69	Rectum	132.1	88	32.3	293.8	3.7	65	38.2	5.1
41c	50	Stomach	113.0	94	40.1	256.0	4.8	71	34.1	3.4
70	43	Rectum	98.2	98	48.0	179.0	4.2	77	38.0	3.4
49	56	Stomach	150.5	107	26.8	420.3	4.3	85	31.2	5.0
54	40	Sigmoid	92.5	112	37.8	224.0	5.0	91	31.2	2.1
56	57	Breast	103.8	118	29.4	212.1	4.2	97	40.7	3.6
57	52	Breast and cervix of uterus	85.2	120	41.5	155.0	4.8	98	38.6	2.6
58	55	Prostate	96.8	120	20.0	191.0	4.4	99	44.7	3.2
59	55	Breast	123.2	123	48.2	245.8	6.0	103	39.2	2.8
71	50	Breast	113.9	124	29.7	216.0	5.9	104	45.4	2.7
61	44	Breast	133.5	130	41.2	280.1	5.7	110	38.5	3.3

blood is plotted as a function of the hemoglobin percentage. In Chart 2, the results obtained in the control cases and the cases of cancer are indicated. In Chart 3, the parallelism between the total phosphorus and the hemoglobin percentage is shown in one case of cancer of the stomach, treated by short wave-length roentgen-ray therapy, and in one case of multiple myeloma, which have been observed over a period of several months.

It might be argued that a closer relationship should exist between the total phosphorus content of the whole blood and the number of red corpuscles in a unit volume of blood or the volumes percentage of red corpuscles than between the total phosphorus content and the hemoglobin percentage. Our data indicate, however, that such is not the case. The closest relationship obtains between the total phosphorus content of the whole blood and the hemoglobin percentage. Yet this relationship is only a general one and many unexplainable exceptions occur. Were the total phosphorus content of the whole blood strictly parallel to the hemoglobin percentage, as future examination of the problem may well show to be the case, then it would follow that *other things being equal*, the phosphorus content of the red corpuscles should be proportional to the color index. Our present results are too few, however, to throw any important light on the apprehension of this problem.

Whatever the ultimate outcome is, it is obvious that the dependence of the total phosphorus content of the whole blood on the hemoglobin percentage is due to the preponderance of phosphorus in the corpuscles. Accordingly, as the number of red corpuscles, and hence ordinarily the hemoglobin content of the blood, increases, an increase in the total phosphorus content of the whole blood is to be expected unless some extraneous factor, e. g., rickets, nephritis or leukemia, etc., permits an undue alteration of the total phosphorus content of the corpuscles and plasma. That this is the case is shown in Tables 3 and 4 under the heading "theoretical" values for the total phosphorus of the whole blood. These values are calculated from the mean normal values for the total phosphorus contents of the plasma and corpuscles and show a very definite approximation to the results obtained by actual analysis.

The situation is entirely comparable to that which obtains in the case of the sodium chlorid content of the whole blood. Norgaard and Gram<sup>13</sup> have shown that, owing to the preponderance of chlorid ion in the plasma, the chlorid content of the whole blood is greater in cases exhibiting anemia than in those with polycythemia. Moraczewski,<sup>1</sup> who published his results about thirty years ago, did not observe this inverse relationship between total phosphorus and sodium chlorid but stated

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13 Norgaard, A., and Gram, H. C. J. Biol. Chem. 49: 263, 1921.

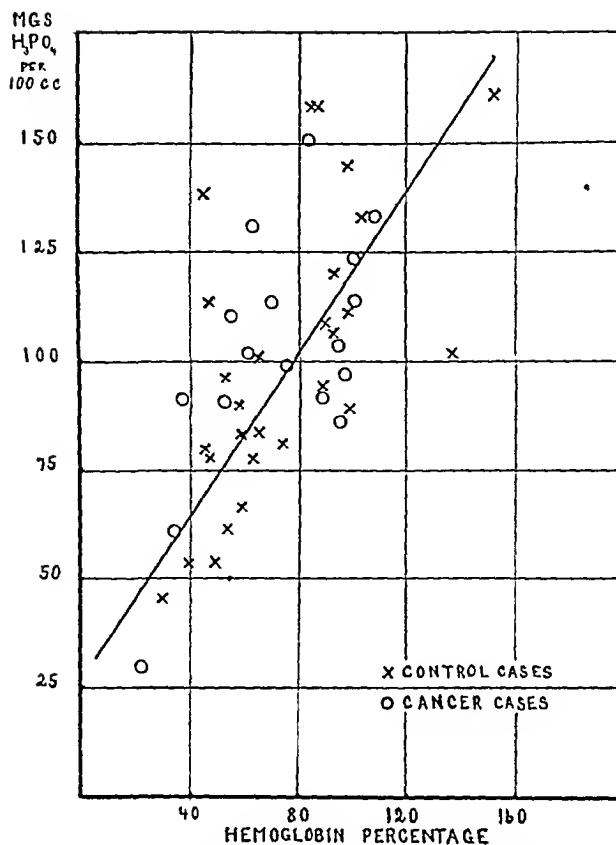


Chart 2—The correlation between the total phosphorus content and the hemoglobin content of the whole blood in all cases. Values for control cases are indicated by crosses and those for cases of cancer by circles. The straight line represents the theoretic values for the total phosphorus content of the whole blood at different levels of hemoglobin content. These values are calculated from the mean normal values for the phosphorus content of plasma and cells, on the assumption that the total phosphorus content of the whole blood is a function of the hemoglobin content.

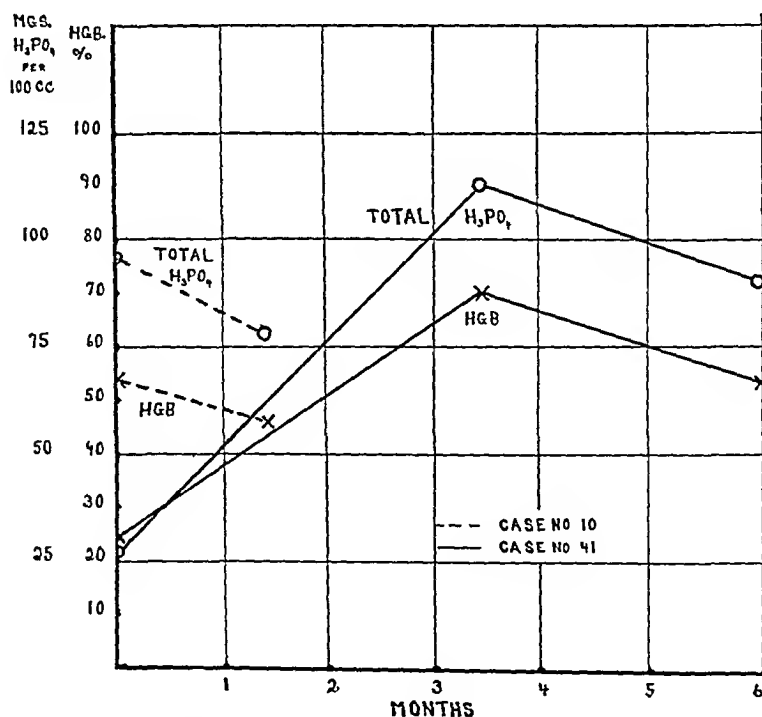


Chart 3—The correlation between the total phosphorus content and hemoglobin content of whole blood in individual cases over a period of months.

that the phosphorus content of the whole blood decreases with a decrease in the sodium chlorid content. Although our studies did not include determinations of the sodium chlorid content of the blood, in view of the modern work of Noirgaard and Gram and our own results with respect to phosphorus, it appears reasonable to expect that as the total phosphorus content of the whole blood rises the sodium chlorid content will fall. Further evidence to suggest that such is the case is that following irradiation Schlagintweit and Sielmann<sup>14</sup> have shown that the sodium chlorid of the plasma falls while we<sup>15</sup> have observed that the phosphorus may rise.

*Phosphorus Quotient*—It is in view of the considerations before mentioned that the phosphorus quotient must be evaluated. As the total phosphorus content of plasma, and of corpuscles in the patients with cancer and in the control cases of our series show no significant variations from each other, it is not to be expected that the phosphorus quotient will be altered in any important way in any one group of cases. As a matter of fact the mean value of the phosphorus quotient for the seventeen patients with cancer was lower (3.40), not higher, as Groebly<sup>2</sup> and Vorschütz and Vorschütz<sup>3</sup> found, than the mean value (3.89) for the twenty-eight control cases.<sup>16</sup>

#### CONCLUSIONS

1 The total phosphorus content and the inorganic phosphorus content of the whole blood, plasma and cells are not significantly altered in cancer.

2 The total phosphorus content of the whole blood is roughly parallel to the hemoglobin content in all persons in whom the values for the total phosphorus in the plasma and corpuscles are within normal limits. This parallelism is due to the preponderance of phosphorus in the red corpuscles. Immature red cells probably contain more phosphorus than adult ones.

3 The phosphorus quotient of Groebly<sup>2</sup> and of Vorschütz and Vorschütz,<sup>3</sup> is of no value in the diagnosis of cancer.

NOTE—Since this paper went to press Zerner<sup>17</sup> has published investigations concerning the relation of the phosphorus quotient to cancer. He recognizes a certain parallelism between the phosphorus content of

14 Schlagintweit, E, and Sielmann, H. Klin. Wchnschr. **1** 2136 (Oct. 21) 1922.

15 To be published.

16 The values we have obtained for the phosphorus quotients as well as for the total phosphorus contents are somewhat higher than those reported by Groebly<sup>2</sup> and by Vorschütz and Vorschütz<sup>3</sup>. The difference is undoubtedly due to difference in the methods employed, and does not influence the conclusions that have been reached.

17 Zerner, H. Ztschr. f. Krebsforsch. **21** 157 (Feb.) 1924.



the blood and the level of the red cell count, but concludes that the phosphorus quotient shows a specific elevation in cancer. Unfortunately, however, only two of his four control cases show any material reduction in the number of red blood corpuscles. It would seem to us that, in the absence of adequate control cases, it is incorrect to attach the significance that he does to his results.

# MESOTHELIOMA OF THE PLEURA

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The histogenesis and classification of primary malignant tumors of the pleura has been the subject of much controversy. Opinion has been divided as to whether they should fall under the class of carcinoma or sarcoma, or be placed in a separate group of endothelioma. The nomenclature of each author has been based rather on his opinion of the type of cell from which the tumor has arisen than on the grounds of the histologic appearance of the growth. Against an embryologic classification of tumors, Ewing<sup>1</sup> urges that we consider the behavior of neoplastic cells as being influenced more by the acquired characters of the cells of origin than by their embryologic derivation. He states that oncology is not a department of embryology, but a separate chapter in the biology of the cell. Similarly, Adler<sup>2</sup> believes that the structure of a tumor is not dependent on its morphologic relation to the three germ layers, but that whatever tumor has the structure of carcinoma and behaves as a carcinoma, is a carcinoma, no matter whether derived from ectoderm, endoderm or mesoderm. Likewise, Marchand<sup>3</sup> believes that extra-uterine pathology should not be tyrannized over by embryology.

Although there is a certain amount of justification for such views, it, nevertheless, is a fundamental fact that tumors exhibit definite characteristics dependent on the embryologic development of the cells from which they arise. A classification based on morphology coincides quite accurately with one based on embryologic development. It is only in the case of tumors arising from cells of mesodermal derivation that there is an apparent discrepancy. The difficulties in the classification of such tumors can only be solved if we recognize the fact that these tumors form a distinct group, outside of the class of carcinoma and sarcoma. They have definite morphologic characteristics dependent on their embryologic development, the cells exhibiting the ability to differentiate in more ways than one, giving a mixed type of growth. The primary malignant tumors of the pleura are a useful illustration of this

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\* From the Department of Pathology, Harvard Medical School, and the Pathological Laboratory, Long Island Hospital.

1 Ewing, J. Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1912, Ed. 2.

2 Adler, I. Primary Malignant Growths of Lungs and Bronchi, New York, Longmans, Green & Company, 1912.

3 Marchand. Cited by Adler, Footnote 2.

fact, and from a study of such tumors it seems permissible to draw certain conclusions with regard to the nature of neoplastic processes occurring in cells of mesoblastic origin

The variety of names applied to malignant pleural tumors indicates how much confusion exists with regard to the nature of the cell from which they are derived. According to many of the older German writers following the lead of Schulz,<sup>4</sup> they are considered to be derived from the endothelium of the subpleural lymphatics and are designated as endothelial carcinoma. Glockner<sup>5</sup> upholds Schulz's view with regard to the derivation from lymphatic endothelium but urges the use of Eppinger's term of "endothelioma" to exclude them from epithelial growths. Bohnheim,<sup>6</sup> Ewing,<sup>1</sup> and many others follow this classification, although there is no conclusive evidence that the lymphatic channels are actively concerned in the process. Others, such as Bloch,<sup>7</sup> believe that these tumors arise from the lining cells of the pleura and likewise call them endotheliomas. Such a classification disregards exact embryologic terms. The majority of writers, including Aschoff,<sup>8</sup> Kaufmann,<sup>9</sup> and Herxheimer,<sup>10</sup> believe that they may arise both from subpleural lymphatics and the "endothelial" cells lining the pleural cavity, and use the term endothelioma to cover both possibilities. On the other hand, Ribbert,<sup>11</sup> Benda,<sup>12</sup> Hanseemann<sup>13</sup> and Gutmann<sup>14</sup> believe that they arise solely from the mesothelial covering of the lung and fall under the general classification of carcinoma. Adam,<sup>15</sup> followed by others, uses the term mesothelioma to indicate more exactly this origin.

The futility of trying to prove the point of origin is evident, so long as it has been impossible to study these tumors in the early stages. It seems, however, logical to believe that they arise from the mesothelial cells lining the serous cavities, as evidenced by their large surface of

4 Schulz, R. Das Endothelcarcinom, Arch f Heilk **17** 1, 1876

5 Glockner, A. Ueber den sogenannten Endothelkrebs der serösen Haute, Ztschr f Heilk **18** 209, 1897

6 Bohnheim, P. Ueber sogenannte primäre Pleuraendotheliome, München med Wchnschr **51** 74, 1904

7 Bloch, M. Le neoplasmes malins primitifs de la plevre, Thesis, Paris, 1905

8 Aschoff, L. Pathologische Anatomie, Jena, Gustav Fischer, 1921, Ed 5

9 Kaufmann, E. Lehrbuch der speciellen pathologischen Anatomie, Berlin, 1904, Ed 3

10 Herxheimer, G., and Reinke, F., in Lubarsch. Ostertag Ergebnisse der Pathologie und Anatomie **16** 225, 1914

11 Ribbert, H. Ueber Pleuratumoren, Virchows Arch f path Anat **196** 341, 1909, Geschwulst-Lehre, Bonn, Cohen, 1904

12 Benda, C. Ueber das primäre Carcinom der Pleura, Deutsch med Wchnschr **23** 324 (May 20) 1897

13 von Hanseemann, D. Atlas der bösartigen Geschwulste, Berlin, 1910

14 Gutmann, C. Beitrag zur Kenntniss der primären malignen Tumoren der Pleura, Deutsch Arch f klin Med **75** 337, 1903

15 Adam, J. G. Principles of Pathology, Philadelphia, Lea & Febiger, 1908

origin, their unique histologic appearance, which is quite different from that of tumors known to arise from lymphatic endothelium, and by the fact that the submesothelial tissues are uninvolved in the process, except by direct invasion

The entire group of malignant neoplasms of the pleura are of rare occurrence. Wagner<sup>16</sup> reported the first case in 1870, not recognizing it as a tumor, but considering it a pseudotuberculous infection. Later, Schulz<sup>1</sup> examining Wagner's case described it as endothelial carcinoma. Since then various cases have been reported, chiefly in the German literature, often as dissertations, under a variety of names. Many of the early cases are doubtful, some lacking microscopic examination, in others a primary tumor elsewhere is not excluded. Glockner,<sup>2</sup> in 1897, made a systematic search of the literature, tabulating and analyzing all cases to date. He considered forty-two cases authentic, and added seven cases of his own. Bloch,<sup>7</sup> in 1905, made a similar analysis of reported cases and considered sixty-three cases (forty-seven endotheliomas and sixteen sarcomas) authentic. Clarkson,<sup>17</sup> in 1914, considered only fifty-one to be authentic.

The rarity of the condition is likewise indicated by the fact that in 10,829 necropsies in the Pathological Institute of Munich, only three cases of primary malignant tumors of the pleura were found (Seydel<sup>18</sup>). In 1911 there were only two cases on record at Johns Hopkins Hospital in 5,000 necropsies (Sprunt<sup>19</sup>).

The case herewith reported is described because of its rarity, and because of certain interesting histologic features, which support the view that tumors arising from cells of mesoblastic origin form a distinct group, having certain individual characteristics which distinguish them from tumors arising from epithelium and connective tissues. Grossly, the appearance conformed to the classical description of so-called endothelioma, in that the entire pleura of one lung was apparently simultaneously involved in a dense, sheetlike extension of tumor enveloping the lung and pericardium. Microscopically, the cells exhibited potentialities of differentiating in several ways. Although the predominating cells were large, spindle cells of fibroblastic type, other cells of epithelial morphology formed channels, while a further step in differentiation was presented by cells which contained large vacuoles, apparently representing actively secretory cells.

16 Wagner, E. Das tuberkelähnliche Lymphadenom, *Arch f Heilk* **11** 497, 1870.

17 Clarkson, F. A. Primary Endothelioma of the Pleura, *Canad M A J* **4** 192, 1914.

18 Seydel. Ueber Operabilität von Lungen- und Pleuratumoren, *München med Wchnschr* **77** 452, 1910.

19 Sprunt, T. P. Primary Carcinoma of the Pleura, *Bull Johns Hopkins Hosp* **22** 289, 1911.

## REPORT OF CASE

*Clinical History*—The patient was a woman, aged 57 years, whose chief complaint was weakness, and pain in the right side of the chest. The family history and previous personal history were unimportant. Just before admission she had fallen, after which she suffered considerable pain in the right side of the chest.

*Physical Examination*—The chief findings were malnutrition, dulness over the whole right side of the chest, with diminished breath sounds, a hard sub-

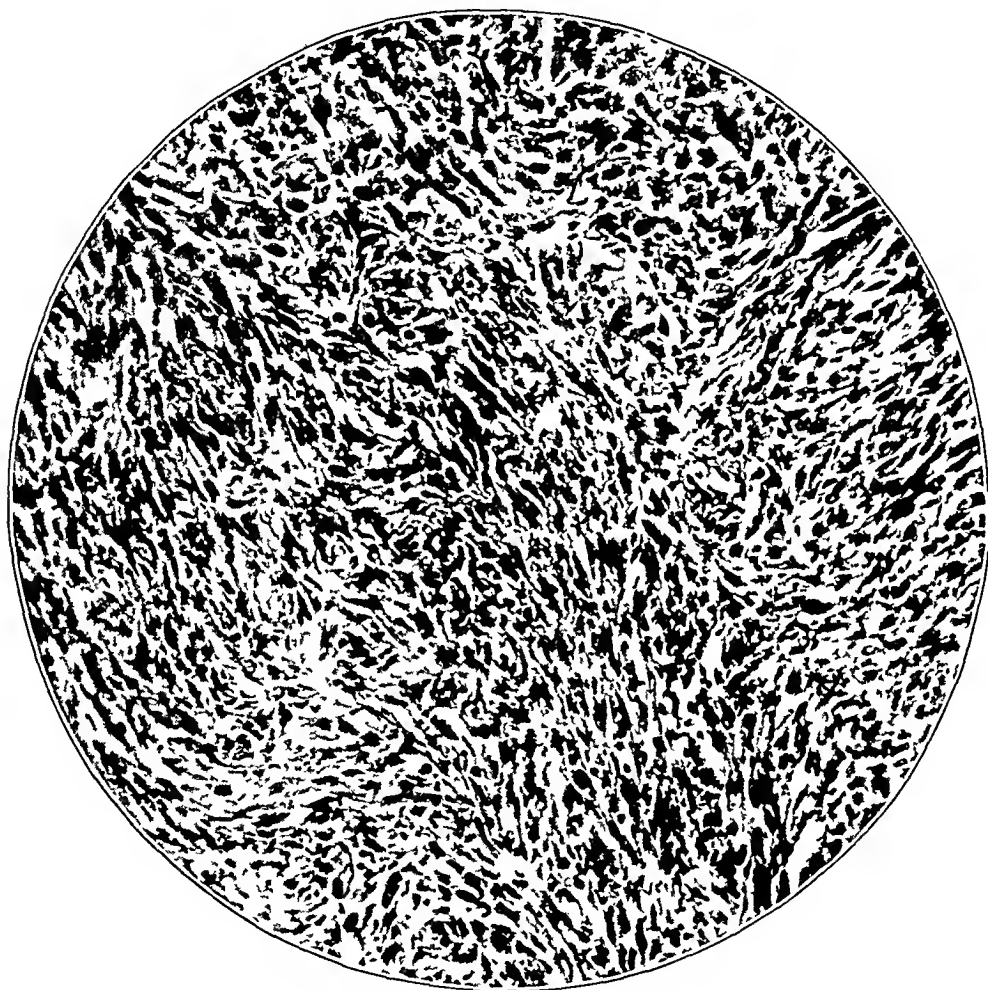


Fig 1—Low power photomicrograph of the tumor enveloping the lung, showing the predominating fibroblastic type of cell forming whorling strands

cutaneous mass overlying the anterior portion of the third fourth and fifth ribs of the right side and enlarged liver. Roentgenogram of the chest showed thickening of the hilum of the right lung and a dense shadow, which was interpreted as encapsulated fluid or an old empyema. The clinical laboratory findings were unimportant. A month after admission the patient became acutely ill, with elevation of temperature and physical signs of consolidation of the right lung. Death occurred on the ninth day.

*Necropsy*—Anatomic Diagnosis. Mesothelioma of pleura (right) with extension to pericardium, thoracic wall, diaphragm, and peribronchial lymph nodes and metastases to cerebral cortex and left adrenal, bronchopneumonia, chronic

passive congestion of liver, herniation of cerebellum through foramen magnum

The body was that of a fairly well developed, poorly nourished white woman. A hard nodular subcutaneous mass was palpable below the right breast and apparently was fixed to the ribs.

On opening the thorax the left lung was voluminous and free of adhesions. The right lung and heart were bound together and the lung bound to the chest wall by a growth of dense tissue, which extended through the intercostal spaces, forming a mass, which was hard and nodular, over the third, fourth and fifth ribs. The lung had to be severed by knife from the thoracic wall.

The pericardial sac was obliterated by a narrow band of dense tissue, 4 mm

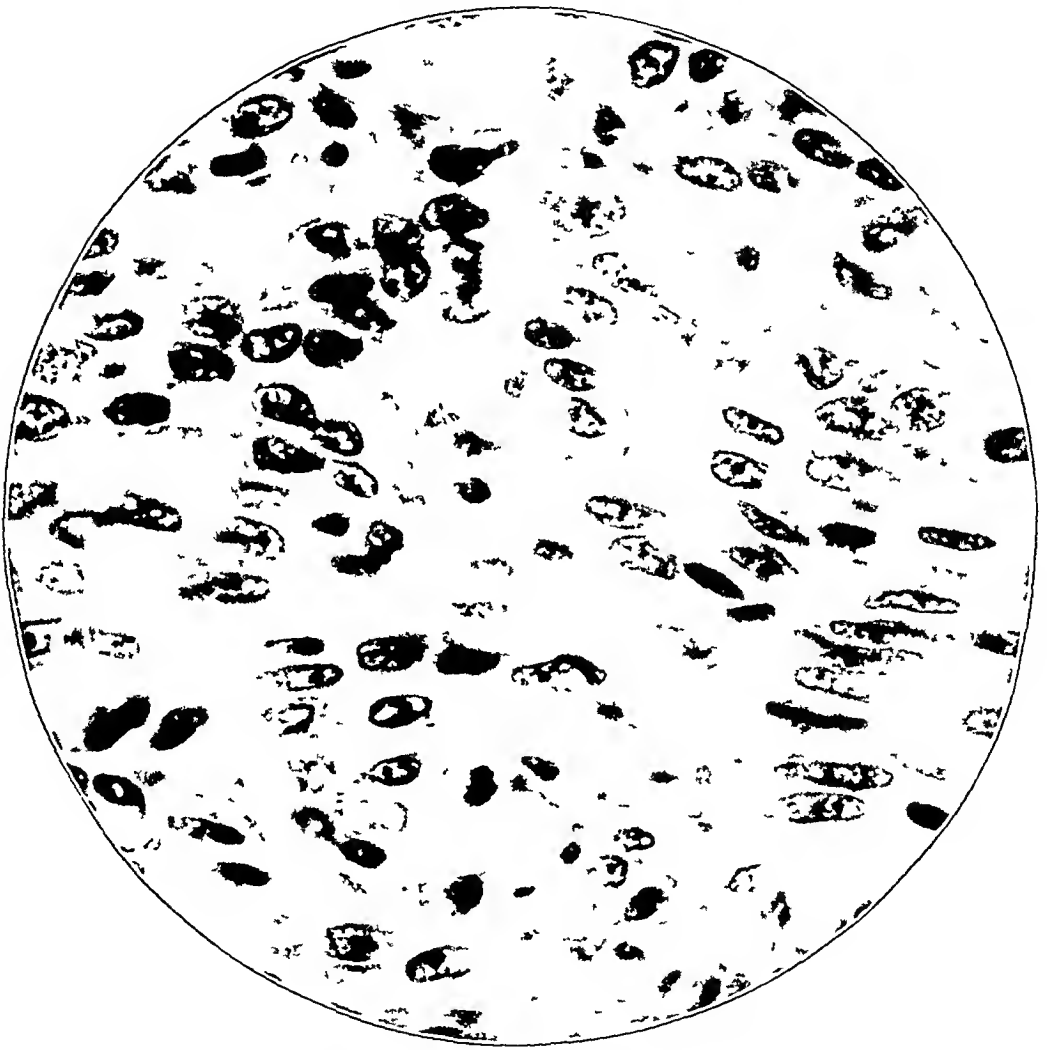


Fig 2—High power photomicrograph of the same section, showing actively proliferating cells of spindle form

in width, extending from the lung and enveloping the myocardium. This tissue did not invade the muscle at any point, but formed a straight line of demarcation, and appeared as an elevated ridge of translucent tissue of almost cartilaginous consistency continuous with the pleura of the right lung. The left lung was distended with air and had a smooth, glistening pleural surface. The pulmonary tissue was crepitant throughout, and the cut surface was pale, dry and spongy. At one point was a small, irregular area of firm gray tissue, suggesting a tumor 0.7 mm in diameter, surrounded by pulmonary tissue. The dependent portions of the lung were dark red, slightly increased in consistency and the cut surface exuded frothy blood.

The right lung and heart together weighed 1,450 gm. The entire right lung was enveloped by a dense, almost cartilaginous sheet of tumor, which was continuous with that described surrounding the heart. This tissue was pale yellow uniformly dense and homogeneous throughout, and formed a layer varying from 1 to 3 cm in thickness. This infiltrated the diaphragm, the tumor here forming a particularly thick layer, and presenting on the peritoneal surface as slightly elevated nodules. The demarcation between tumor and lung was irregular in contour but sharply defined. At times it formed wedge-like extensions into the interlobar fissures, but only at one point was there a slight penetration into pulmonary tissue. A circumscribed spherical mass of tumor

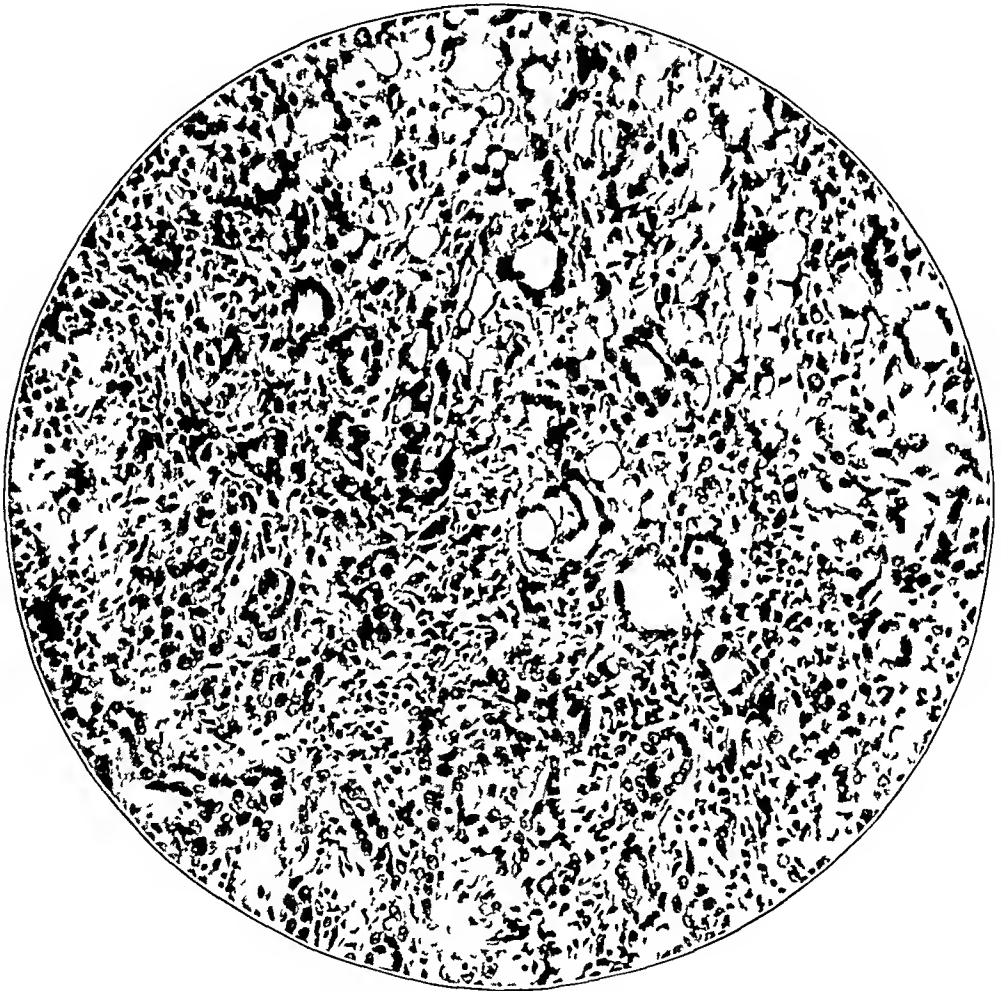


Fig 3—Tumor growing into an interlobar septum, where the tumor cells are of epithelial morphology, and are forming intercommunicating channels. A further step in differentiation is illustrated where signet ring cells, appearing at first sight as fat cells, occur among those of epithelial and fibroblastic type (Low power.)

tissue, 3 cm in diameter, lying in close relation to the arch of the aorta, of soft consistency, appeared to represent an involved lymph node. The tumor continued over the root of the great vessels to the pericardium and invaded extensively the mediastinal fat. The pulmonary tissue showed yellow granular areas of consolidation throughout which coalesced, while the intervening tissue was dark red. The bronchial mucosa was injected and roughened.

The left adrenal showed at one pole a mass of tumor tissue measuring 3 by 2 by 2 cm. This was pale gray, quite firm and homogeneous and was almost completely surrounded by adrenal cortex.

The other abdominal structures showed no lesions of interest. On examination of the brain, the right fissure of Sylvius, and part of the right temporal lobe were occupied by a firm nodule of tumor tissue 1.5 cm in diameter which penetrated the cortex. The left temporal lobe showed a similar nodule, 1 cm in diameter, of equal firmness. The cerebellum was herniated through the foramen magnum.

The spinal cord presented no gross lesion, and the vertebrae showed no evidence of metastases.

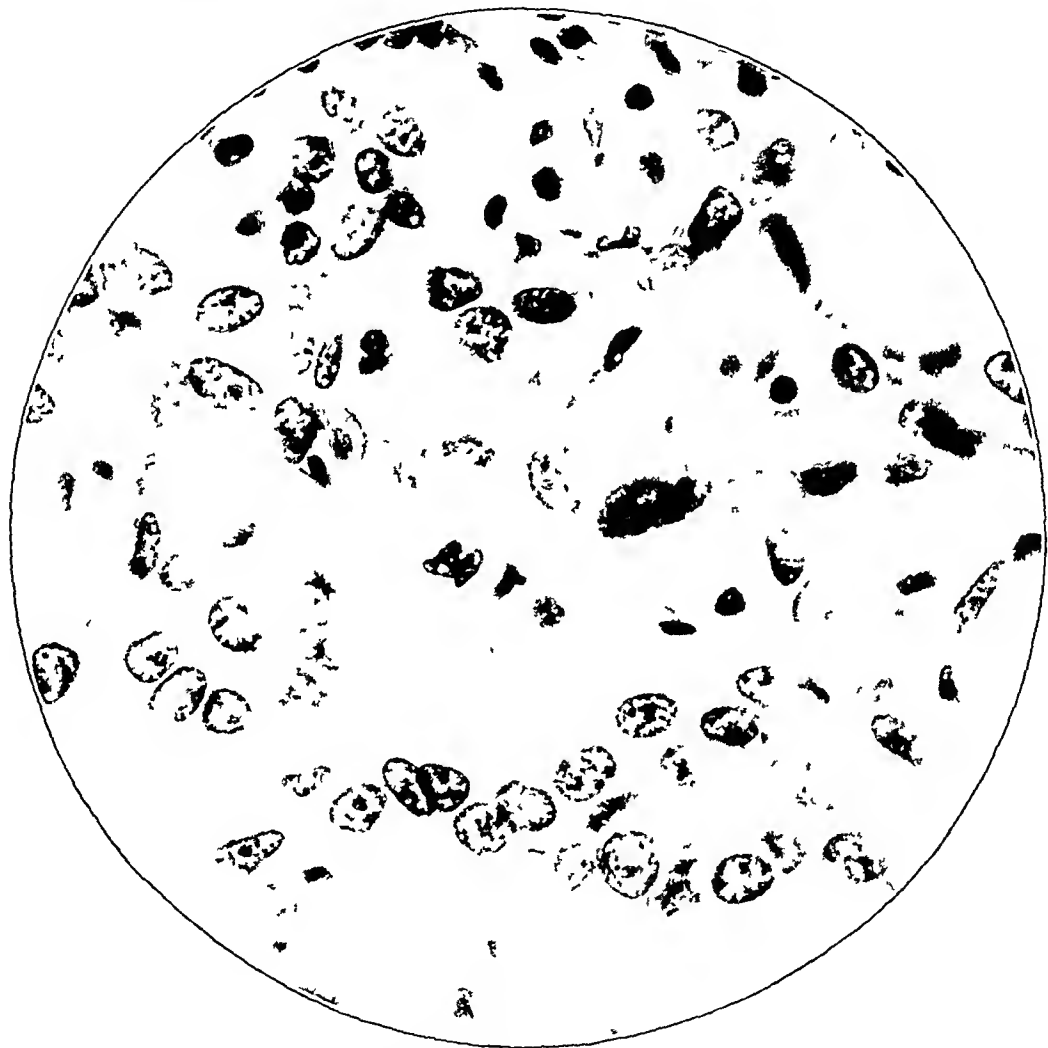


Fig 4—High power photomicrograph of Figure 3, showing the character of the epithelial-like tumor cells.

*Microscopic Examination*—Tumor. Where the growth was of moderate density, such as where it involved the surface of the lung in relation to the mediastinum, it was largely composed of spindle shaped cells (Fig 1). These were of an actively proliferating type, ran in various directions, and formed whorling strands. Many of the cells were large, with abundant cytoplasm, and tapered off gradually at both poles into filaments (Fig 2). The nuclei were large and hyperchromatic. Mitotic figures were very numerous. Occasional giant multinucleated forms occurred.

The densest portions of the tumor, where it involved the diaphragm and lateral portions of the chest wall, was composed largely of hyalinized connective tissue. However, areas persisted where actively growing cells occurred.



Where the tumor was growing into an interlobar septum, the cells assumed an entirely different character and higher degree of differentiation (Fig 3) Here they were oval or cuboidal and formed narrow cords and intercommunicating channels They were distinctly of epithelial morphology, with abundant cytoplasm and round vesicular nuclei (Fig 4) Although arranged in fairly regular alinement, the cells were actively hyperplastic and contained many mitotic figures A further differentiation appeared to have occurred Cells appearing at first sight as fat cells were interspersed among those of epithelial and fibroblastic type (Figs 3 and 5) They were of signet ring appearance, a large globule occupying most of the cytoplasm with the nucleus placed in the

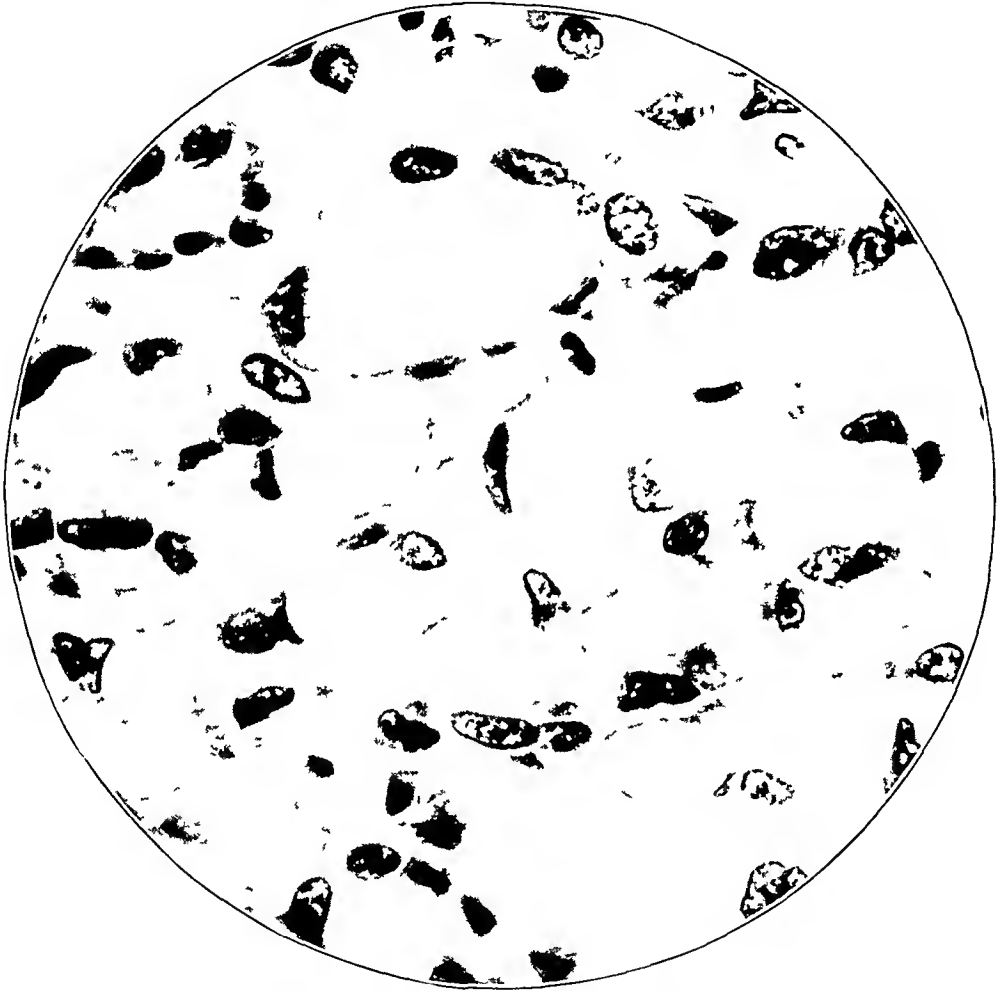


Fig 5—High power photomicrograph of Figure 3, showing that the signet ring cells consist of large globules of secretion displacing the nuclei to the side Transition forms are seen between these cells and the epithelial-like cells forming channels

periphery Their nuclei were indistinguishable from the nuclei of the adjacent epithelial-like cells In frozen sections stained with scarlet red, these globules failed to react for fat, and appeared as highly refractile droplets quite similar in appearance to the goblet cells of the intestinal tract These globules were undoubtedly secretion products, and the cells at times proliferated around their own secretions, thereby forming what appeared to be lumina

A definite transition could be discerned between these three different types of cells In this transition zone, the cells containing vacuoles and forming

pseudolumina gradually were transformed to more cuboidal epithelial-like cells forming more definite channels, and containing only small vacuoles or none at all. At a point beyond this, the epithelial-like cells assumed spindle forms but were loosely and irregularly arranged. Beyond this the spindle cells tended to lie parallel to each other and formed whorling strands similar to the growth elsewhere.

The same combination of the three types of cells was seen in the peribronchial lymph nodes. Here the predominating cells were small and oval, tending only slightly to long, spindle cell forms. They were quite uniform in size and contained oval, vesicular nuclei which presented but few mitotic

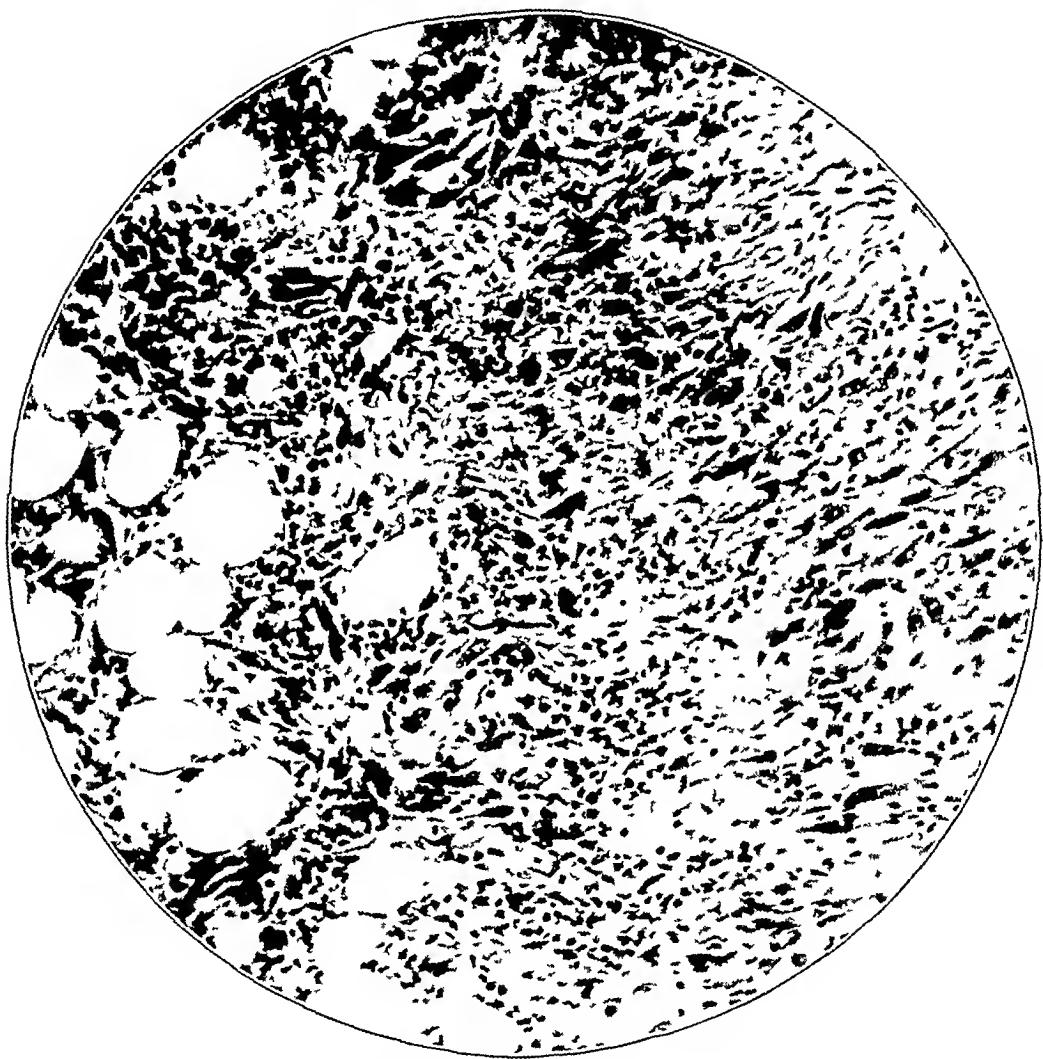


Fig 6—Tumor ensheathing heart and invading epicardial fat

figures. The cells were closely placed with very little intervening stroma. In certain portions, however, small vacuoles were seen which appeared at times as cytoplasmic inclusions, but more often appeared as signet ring forms, with large active nuclei morphologically similar to those of the other tumor cells. At the same time the cells tended to become cuboidal and arrange themselves in rows simulating channels. Apparently wherever the cells gave evidence of less rapid growth, not only was there formation of channels but the cells appeared to have secretory activity.

Where the tumor ensheathed the heart (Fig 6), the cells were of a rapidly proliferating type, as a rule of spindle form. Many large cells were present,

with elongated, hyperchromatic nuclei, containing an acidophilic nucleolus. Mitotic figures were numerous. The cells, though invading the epicardial fat, in no place penetrated the heart muscle but formed an enveloping layer quite uniform in width.

One section showed a portion of the pleura where there occurred stretches of intact mesothelial cells covering the lung, separated by a space from the overlying tumor. This was interrupted by areas where the tumor had become adherent, with disappearance of the mesothelial cells.

Sections of the metastases in the adrenal and in the opposite lung showed essentially cells of spindle form, running at various angles, and similar in morphology to those occurring in the pleural tumor, where it was of moderate density. In the metastases there was no tendency to the development of epithelial forms.

Microscopic sections of the other organs showed no lesions relevant to the tumor process.

A review of previously reported cases of primary malignant tumors of the pleura reveals the fact that although the various authors have classified their tumors as endotheliomas, carcinomas, or sarcomas, in actual point of fact their descriptions are strikingly similar, and indicate a wide range of cell types occurring in a single tumor with cells of epithelial morphology usually predominating. Although it would seem that all these tumors represent essentially the same process, yet because of minor differences the cases as described by the authors arrange themselves into three groups.

1 A few cases, such as those of Benda,<sup>12</sup> Sprunt<sup>19</sup> and Bayne-Jones,<sup>20</sup> are almost purely epithelial in character. In Benda's and Sprunt's cases, villi invested by columnar cells projected from the surface and appeared to be continuous with the mesothelial cells of the pleura. In Bayne-Jones' case cylindric cells were arranged in glandular formation. The epithelial elements were so prominent that the authors made the diagnosis of carcinoma, arising from the lining cells of the pleura.

2 In the second group, which comprises the majority of reported cases, the cells described are of varied type, cuboidal or columnar cells forming channels and solid cords, combined with polymorphous and spindle shaped cells. In interpreting this appearance, the authors stress the fact that the predominating cells are of epithelial type, speaking of them as "epithelial-like" and "epithelioid," and yet they consider that these are endothelial cells, and almost invariably interpret anastomosing channels lined by these cuboidal cells as evidence of the fact that the cells are derived from lymphatics and in their growth are simulating lymphatic channels. This appearance could just as well be interpreted as due to epithelial cells assuming glandular arrangement. Similarly,

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20 Bayne-Jones, S. Carcinoma of the Pleura with Hypertrophic Osteo-Arthropathy, *Johns Hopkins Hosp Reports* 18 213, 1919.

tumor cells lying in lymphatic channels are continually given as evidence that these cells have arisen from lymphatics, whereas it seems more plausible to consider that these tumor cells are permeating lymphatics, especially since metastases of these tumors are known to occur chiefly through the lymphatics

It is apparent that the various writers have been prejudiced in their descriptions by their *a priori* conclusions that these tumors are derived from lymphatic endothelium, and this makes an analysis of old cases almost impossible, as even drawings of microscopic sections are made diagrammatically to represent origin from lymphatics. The more recent cases are less difficult to interpret, as photomicrographs often indicate cells of true epithelial morphology even though the writers describe them as being of endothelial character. A typical example of this sort of description and interpretation is found in a report of Bassoe,<sup>21</sup> who describes "gland-like tubules," which in photomicrographs appear as epithelial cells, but which he says represent "an apparently unbroken chain of proliferating lymphatic channels," the cells which "simulate cylindric epithelium" and "give to lymphatic channels the appearance of gland tubules"

The idea of lymphatic origin seems to be a tradition handed down from writer to writer, each one following his predecessor in descriptions and interpretations of striking similarity. The chief characteristics of these tumors appear in most descriptions, namely, the varied type of cell, predominatingly of epithelial morphology with formation of tubules, but often combined with polymorphous and spindle forms. Cases apparently of this type include those recorded by Schulz,<sup>4</sup> Wagner,<sup>10</sup> Bohnheim,<sup>6</sup> Bloch,<sup>7</sup> Fraenkel,<sup>22</sup> Adler,<sup>23</sup> Delafield,<sup>24</sup> Gutman,<sup>14</sup> Glockner,<sup>5</sup> Harris,<sup>25</sup> Huismans,<sup>26</sup> Keilty,<sup>27</sup> Kornitzer,<sup>28</sup> Leiseur, Savy

21 Bassoe, P. Report of a Case of Primary Tumor of the Pleura, Tr Chicago Path Soc **6** 31, 1903

22 Fraenkel, A. Zur Klinik der Lungen- und Pleurageschwulste (Endothelioma Pleurae), Deutsch med Wchnschr **37** 531 (March 23) 1911

23 Adler, I. Remarks on Primary Endothelioma of Lungs and Pleura, J M Res **1** 175, 1901

24 Delafield, F. The Primary Newgrowths of the Pleura, M Rec **62** 761, 1902

25 Harris, T. Primary Malignant Diseases of the Pleura, J Path & Bacteriol **2** 174, 1893

26 Huismans, L. Zur klinischen und pathologisch-anatomischen Diagnose maligner Pleuratumoren (Karzinom oder Endotheliom), Deutsch med Wchnschr **38** 1278 (July 4) 1912

27 Keilty, R. A. Primary Endothelioma of the Pleura, Am J M Sc **153** 888 (June) 1917

28 Kornitzer, E. Zur Kenntniss der Pleuratumoren, Berl klin Wchnschr **56** 1039, 1919

and Mazel,<sup>29</sup> McDonnell and Maxwell,<sup>30</sup> Lewis,<sup>31</sup> Pitt,<sup>32</sup> Rosenbaum,<sup>33</sup> Scagliosi,<sup>34</sup> Schulz-Vellinghausen,<sup>35</sup> Unger,<sup>36</sup> Eastwood and Martin,<sup>37</sup> Dubray and Rosson,<sup>38</sup> Bernstein<sup>39</sup> and Volkmann<sup>40</sup>

3 In a smaller group of cases are described growths of sarcomatous nature. Such are the cases of Bernard,<sup>41</sup> who describes cells of large spindle and polymorphous forms, of Dorendorf,<sup>42</sup> in which the growth was composed largely of spindle cells with well developed fibrils, of Mehrdorf,<sup>43</sup> in which the diagnosis of fibrosarcoma myxomatodes was made, of Pallasse and Roubier<sup>44</sup> in which were spindle cells typical of fibrosarcoma.

Many cases called sarcoma, as the cases of Saundby,<sup>45</sup> Podack,<sup>46</sup> Coenen<sup>47</sup> and Greenish,<sup>48</sup> do not materially differ in microscopic appear-

29 Leiseur, Savy, Mazel. Tumeur maligne primitive de la plevre, Arch de med exper et d'anat path **25** 392, 1913

30 McDonnell, P J, and Maxwell, E S. Endothelioma of the Pleura, J A M A **74** 168 (Jan 17) 1920

31 Lewis, D D. Endothelioma of the Pleura, Tr Chicago Path Soc **6** 256, 1905

32 Pitt, G N. Primary Carcinoma of the Pleura, Tr Path Soc London **39** 56, 1887-1888

33 Rosenbaum, S. Beitrag zur Frage der onkologischen Stellung des sogenannten Endothelkrebses der Pleura, Ztsch f Krebsforsch **14** 543, 1914

34 Scagliosi, G. Ueber der primären Krebs der Pleura, Deutsch med Wchnschr **30** 1715 (Nov 17) 1904

35 Schulz-Vellinghausen. Beitrag zur Kenntniss des primären Endothelkrebses der Pleura, Munchen med Wchnschr **47** 647, 1900

36 Unger, K. Zur Klinik des primären Endothelioms der Pleura, Wien klin Wchnschr **16** 1457, 1903

37 Eastwood, E H, and Martin, J P. A Case of Primary Tumor of the Pleura, Lancet **20** 172 (July 23) 1921

38 Dubray, E S, and Rosson, F B. Primary Mesothelioma of the Pleura, Arch Int Med **26** 715 (Dec) 1920

39 Bernstein, H S. A Case of Primary Malignant Disease of the Pleura, Albany M Ann **34** 88, 1913

40 Volkmann, R. Ueber endotheliale Geschwulste, Deutsch Ztschr f Chr **41** 1, 1895

41 Bernard. Zur Kenntniss der Pleurasarkome, Virchows Arch f path Anat **211** 156, 1913

42 Dorendorf, H. Demonstration eines grossen Pleuratumors, Deutsch med Wchnschr **40** 225 (Jan 29) 1914

43 Mehrdorf, R. Fibrosarcoma myxomatodes, Virchows Arch f path Anat **193** 92, 1908

44 Pallasse, E, and Roubier, C. Les Tumeurs primitives de la plevre, Ann de med **3** 243 (May-June) 1916

45 Saundby, R. Three Cases of Sarcoma of the Pleura, Birmingham M Rev **25** 34, 1889

46 Podack, M. Zur Kenntniss des sogenannten Endothelkrebses der Pleura und der Mukormykosen in menschlichen Respirationsapparat, Deutsch Arch f klin Med **63** 1, 1899

47 Coenen. Ein sehr grosses Sarkom der rechten Brustwand, Berl klin Wchnschr **55** 1061, 1918

48 Greenish, R W. A Case of Primary Sarcoma of the Pleura, J Anat & Physiol **75** 337, 1882

ance from those described as endothelioma or carcinoma, the term sarcoma being used merely to express the conviction of the writer that they should be considered of connective tissue origin, rather than on the basis of any histologic difference

Robertson<sup>49</sup> believes that most of these tumors are not primary tumors of the pleura, but are secondary growths from a primary carcinoma elsewhere. However, it is difficult to explain on this basis the fact that the tumor is approximately of the same age over the whole surface of the pleura, this fact, on the contrary, giving evidence of primary growth from multiple foci of origin, in which the whole pleural surface is participating as a unit in the neoplastic process

#### COMMENT

The case reported in this paper falls within the second group, and illustrates well the variety of cell types which occur in close relation to each other. Vacuoles, such as appeared within certain of the cells, are not of frequent occurrence. Podack describes two cases showing refractile globules within the cells which pressed the nuclei to the side, and interpreted them as inclusions. Herxheimer saw similar vacuoles giving the cells a signet ring appearance. Those seen in the present case seem to represent secretory activity, and occur where the tumor cells show a higher degree of differentiation.

Although the varied type of cells is described in almost all reported cases, a few authors have called particular attention to this mixed type of growth. Thus, Bohme<sup>50</sup> emphasizes this character by designating his tumor "sarco-carcinoma," and Gutman, in describing a tumor, states that it has both the character of a carcinoma and a fibrosarcoma. Bloch, and most writers who recognize the mixed character of the growth, assume that several elements in the pleura, such as endothelial cells and connective tissue, are participating in the process simultaneously. This would seem the wrong conception of the process. The pleomorphic nature of the growth is its distinguishing feature and warrants its classification in a group separate from sarcoma and carcinoma, without necessitating the assumption of an origin from two types of cells. The different types of cells occurring in the tumor here recorded are quite evidently closely related. Transitions are seen from one type to another. It is inconceivable that these different forms arise from more than one type of cell, that is, that the cells forming channels arise from epithelial cells, and the spindle cells from fibroblasts. The logical point of view would seem to be that the cells have arisen from a multipotential cell

49 Robertson, H. E. Primary "Endothelioma" of the Large Serous Cavities. *Proc. Am. A. Pathol. & Bacteriol.* (March) 1923, *J. M. Res.* **44** 115 (Sept.) 1923.

50 Bohme, M. Primäres Sarco-carcinom der Pleura, *Virchows Arch. f. path. Anat.* **81** 181, 1880.

which has differentiated now in one way, toward the epithelial type, now in another way, toward the fibroblastic, due to the fact that the mesothelial cells, in undergoing a neoplastic process, have reverted to a more embryonal type, and have the potentialities of embryonal mesoblastic cells in differentiating in more ways than one

A change in cell morphology is commonly seen in various tumors known to arise from a single type of cell. Metastases of epitheliomas may show less differentiation than the growth at the original site, assuming spindle forms. If such change of form occurs in tumors arising from simple epithelium, it is consistent that a change in cell form would more readily occur in tumors derived from cells of mesodermal or mesenchymal origin. The process is well illustrated in mixed tumors (embryomas) of the kidney, as well as those of the serous linings.

The efforts at classifying such tumors, according to whether they are of epithelial or fibroblastic type would seem ill advised. The variety of cell types occurring in a single process indicates that the cell of origin is multipotential. To call these tumors carcinomas or sarcomas would be to make the erroneous implication that the cells conform to one type only. To call them sarcomas is a confusion of ideas, as this implies that there are two cells of origin undergoing neoplastic transformation side by side, whereas the true nature of the process seems to be that one type of cell is differentiating in different directions at the same time. That sometimes cells of epithelial morphology predominate, at other times those of fibroblastic form, is merely a variation in the process which does not alter the nature of the tumor. It would seem advisable to adopt a new name for such tumors, and no longer attempt to place them arbitrarily under groups of carcinoma and sarcoma. Adam's classification of mesolepidomas and mesohylomas is a consistent embryologic one, although a somewhat cumbersome terminology. Until a more perfect nomenclature is devised, it would seem expedient to call all tumors arising from serous linings mesotheliomas, irrespective of which type of cell predominates in the growth.

#### SUMMARY

1 A case is reported of primary malignant tumor of the pleura, enveloping the heart and producing metastases in the cerebrum and adrenal.

2 Microscopically, the cells present three distinct types, spindle cells of fibroblastic morphology, epithelial-like cells forming channels, and cells producing globules of secretion. Transitions were made out between the three types, giving evidence that the cell of origin was a multipotential cell, which had the ability to differentiate both toward the epithelial and toward the fibroblastic type.

3 Reasons are presented for considering primary malignant tumors of the pleura as being derived from the mesothelial cells of the pleura. Tumors derived from such origin should be considered in a class apart as mesothelioma, and not classified as endothelioma, carcinoma or sarcoma.



# THE CLINICAL VALUE OF THE SERUM-TETRACHLORPHENOLPHTHALEIN TEST FOR LIVER FUNCTION<sup>1</sup>

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We have used Rosenthal's simplification of the tetrachlorphenolphthalein method of testing liver function<sup>1</sup> in over 100 cases. In the majority of these patients, the diagnosis has ultimately been confirmed by operation, necropsy or unmistakable clinical course. On the whole, the test has not disappointed expectations, although sharp limitations have been found to its practical usefulness and a number of interesting problems have been encountered.

We have followed Rosenthal's technic except that in the course of the work we have slightly increased the dose of tetrachlorphenolphthalein used, first to 6 and then to 7 mg per kilogram of body weight. We did this in the hope that the doubtful results, which were obtained with 5 mg in cases in which it was fair to assume that slight liver injury existed, would show clear cut results with the larger amount of dye. Our work is sufficient to show that there is no disadvantage in this procedure, it does not give false positive results and the injection of the slightly larger amounts is absolutely harmless. It should be noted that in changing the amount injected we have not changed, in the slightest way, the technic of making the color scale for the final readings, it is necessary to keep this the same in order to compare the two methods.

There was surprisingly little difference between the tests with 5 mg and those with 7 mg. On looking over the general summary of our findings we believe that with either method the presence of 5 per cent of the dye in the one hour specimen may be considered a suspicious sign of impairment of the liver function, while the presence of 8 per cent, or more, of the dye in the one hour specimen may be regarded as conclusive of impaired liver function.

There is one point in technic which cannot be stressed too much, namely, the absolutely unreliable character of the readings if the serum obtained contains traces of dissolved hemoglobin. For this reason the needles used in obtaining the blood must either be dry or must be boiled

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1 Rosenthal, S M. A New Method of Testing Liver Function with Phenol-tetrachlorphthalein. J A M A **79** 2151 (Dec 23) 1922

in a saline solution. The blood obtained must be allowed to stand quietly until the clot has retracted. It is unwise to try to separate the serum by immersing the clot, or by centrifuging before spontaneous retraction of the clot has occurred. In spite of these precautions a little hemolysis may occasionally occur in one of the tubes, for this reason we now make a practice of obtaining two samples in two separate tubes of the fifteen minute and of the one hour specimen, so that if a little accidental hemolysis occurs in the one tube we may still be able to make the readings with the other.

Bloom and Rosenau<sup>2</sup> have recently proposed a modification of the technic, which promises to do away with difficulties from hemolysis. It depends on precipitation by acetone. We have not yet given it sufficient trial to be able to express an opinion on it.

We have seen no toxic effects of the intravenous injections. Many of the patients experienced a burning sensation in the roof of the mouth while the injection was being made. This was followed often by a general sense of warmth. The dye is irritating to the tissues, and any leakage outside of the vein is followed by a sharp local reaction. In giving the injections, if there is the slightest resistance to the plunger of the syringe the needle is not satisfactorily in the vein, it should be withdrawn and reintroduced.

Although we followed Rosenthal's technic, obtaining a sample of blood fifteen minutes after the injection and again after one hour, our experience leads us to believe that, as Bogen<sup>3</sup> has suggested, the fifteen minute examination can safely be omitted. This would make the test easier from the patient's point of view.

We will discuss our material under the following heads:

*Clinical Results*—1 Cases of liver disease (a) cirrhosis, (b) syphilis, (c) catarrhal jaundice, infectious jaundice (Weil's disease), acute yellow atrophy, (d) malignant growths, (e) echinococcus cyst, (f) cholecystitis, (g) obstructive jaundice (persistence of dysfunction)

2 Cases of possible functional impairment of liver (a) pneumonia, (b) myocardial insufficiency, (c) splenomegaly, (d) hemolytic icterus, (e) pernicious anemia, (f) leukemia and Hodgkin's disease

3 Control cases—no liver disease

*General Value in Diagnosis*—(a) Interpretation of results as affected by jaundice, (b) positive value of the test, (c) negative value of the test, (d) cases in which the test failed, (e) comparison with other tests

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2 Bloom, W., and Rosenau, W. H. A Simple Method for the Determination of Phenoltetrachlorophthalein in Blood Serum, *J. A. M. A.* **82**: 547 (Feb. 16) 1924

3 Bogen, E. *J. Lab. & Clin. Med.* **8**: 619 (June) 1923

## CLINICAL RESULTS

## 1 Cases of Liver Disease —(a) Cirrhosis of the liver

There were four cases of typical cirrhosis of the liver. There was unmistakable retention of the dye in all. Of the four patients, three did not show any icterus at the time of the test either in the skin, conjunctiva or blood serum, while one patient was icteric and showed a blood bilirubin of 1/30,000 by the method of Van den Bergh. This case, strangely enough, did not show as high a percentage of tetrachlorophenolphthalein in the blood as did the cases without jaundice.

Besides the cases of typical cirrhosis there was one in which the diagnosis was portal thrombosis, resulting from an abscess of the spleen. This patient (Case 5, Table 1) was originally admitted to the surgical department, with a history of pain in the left side and recurrent fever

TABLE 1—*Atrophic Cirrhosis*

Case No		Mg In- jected per Kg of Body Weight	Percentage of Dye in Blood After		Liver Enlarge- ment	Icterus	Blood Bili- rubin
			15 Minutes	60 Minutes			
Typical Cases							
1	Advanced cirrhosis January 5	5	12	12		0	0
	January 21	5	10	10	+		
	(necropsy) September 21	7	12	15			
2	Advanced cirrhosis	5	10	10	+	+	1 30 000
3	Typical cirrhosis First paracente- sis at time of test Necropsy four months later advanced cir- rhosis and healed duodenal ulcer	7	13	12	+	0	0
4	Typical cirrhosis Repeated para- centesis Spleen enlarged	7	15	15	0	0	0
Atypical or Doubtful Cases							
5	Portal thrombosis (?) following splenic abscess Ascites Recovery	9	8	7	+	0	0
6	Suspected cirrhosis, splenic en- largement	7	10	8	+	0	1 400,000
7	Suspected cirrhosis alcoholism	7	10	5	0	0	1 200,000

of a septic type, was operated on and a large abscess containing the necrotic spleen was opened and drained. After recovery and the healing of the wound the patient developed ascites and emaciation, and presented a clinical appearance indistinguishable from that of ordinary hepatic cirrhosis. Following tapping of the abdomen, which had to be done repeatedly, the large and a densely hard liver could be felt. After some months in the hospital the ascites ceased to recur, the general condition of the patient improved greatly and he went home apparently well. During the period of ascites he developed a very extensive phlebitis of the left leg. Following the injection of tetrachlorophenolphthalein the patient likewise developed phlebitis of the median basilic vein. He was one of the five patients in all our whole series that developed phlebitis after injection, and we believe that in this instance it was due to the tendency to phlebitis already shown in the leg. This case (No 5, Table 1) showed a mild degree of retention (7 per cent at the end

of one hour) 'Due to a miscalculation, the amount of dye injected was 9 mg per kilogram of body weight instead of the usual 7 mg. Our experience in the comparison of the 7 and 5 mg however, has led us to believe that this does not make a great deal of difference. It was unfortunately not permissible to repeat the test on account of the phlebitis.

In addition to these cases there were two others (6 and 7, Table 1), which probably can be classified as early cases of cirrhosis of the liver, although the diagnosis is not certain. The first patient was a man, aged 48, who entered the hospital merely because of heaviness in the flanks lasting for two months. Examination showed the liver enlarged to 3 cm below the free border in the midclavicular line, the spleen enlarged to 3 cm below the free border. Except for an increase to 6 per cent of the eosinophil cells in the blood, a very full set of laboratory investigations gave completely negative results. The serum showed no increase in bile (blood bilirubin 1:400,000). The tetrachlorophenolphthalein test showed a slight retention, 8 per cent at the end of one hour.

The second case (No. 7) was a man, aged 48, a very heavy drinker for many years, who was under treatment for alcoholic gastritis of a year's duration. His test showed slight retention, 10 per cent at fifteen minutes and 5 per cent at one hour.

If other investigators continue to confirm our opinion that the tetrachlorophenolphthalein test never gives false positive results but invariably means some liver disability, it should prove of real value in detection of early cases of cirrhosis of the liver, a condition which at present is quite beyond diagnosis. It will take a good deal more work to prove this definitely.

*Syphilis of the Liver* —There were five patients with syphilis of the liver. In four of them the diagnosis rested on clinical grounds, as it was impossible to obtain confirmation by necropsy or operation, nevertheless, the clinical signs were sufficiently convincing to leave the diagnosis in little doubt. When the results of the tetrachlorophenolphthalein tests were compared the cases were seen to fall into two sharply opposed groups. The two cases of congenital syphilis in the young both showed marked dye retention. This agrees with the well known pathologic changes of congenital syphilis of the liver, which consists of a diffuse intercellular cirrhosis.

On the other hand the three cases of syphilis of the liver in adults all showed normal liver-function tests. This agrees well with the pathology, which consists of scattered gummas and secondary scar formation, occurring probably over a considerable period of years, as the slow course allows ample time for liver regeneration, one would only expect impaired liver function if the process was very extensive, or

accidentally cut off circulation or bile drainage from large areas. This is well illustrated by Case 5 (Table 2), in which, because of secondary infection of a gumma, a laparotomy was necessary. The patient, a man, aged 47, gave a history of a similar attack of pain and fever four years before. He was admitted to hospital, with a history of being ill only four days with fever and severe epigastric pain. There was a tender mass in the right upper quadrant of the abdomen, evidently on the dome of the liver, which was enlarged to the umbilicus. At operation there were many large scars on both upper and lower surfaces of the liver, and an abscess, apparently an infected gumma on the dome. This was sutured to the abdominal wall and incised five days later. It gave a culture of *B. coli*. The blood Wassermann reaction was positive (four plus). In spite of the gumma and the numerous scars the functional test was normal.

TABLE 2—*Syphilis of the Liver*

Case No		Wasser mann Reaction	Mg In jected per Kg of Body Weight	Percentage of Dye in Blood After		Liver Enlarge ment	Icterus	Blood Bili- rubin
				15 Minutes	60 Minutes			
In Children								
1	Congenital, 6 years old	Neg	5	13	13	+	Slight	1 300 000
2	Congenital, 2½ years old	Neg	7	15	20	+	Subicteric	1 60,000
In Adults								
3	Acquired syphilis, man, 59	Neg	7	5	Trace	+	0	1 300 000
	Large, hard irregular liver Spleen enlarged		7	7	Trace		0	1 300,000
4	Probable congenital syph- ilis Interstitial kera- titis, 52 years old, gum- matous scars of liver	Four plus	7	5	Trace	+	0	1 200,000
5	Acquired syphilis, 47 years old, infected gumma (operation) Deep liver scars	Four plus	5	5	Trace	+	0	0

*Catarrhal Jaundice, Acute Yellow Atrophy, Infectious Jaundice (Weil's Disease)*—These three conditions are grouped together because there was only one case of each, and because recent work has indicated a close relation in the pathogenesis of the conditions.

The case of catarrhal jaundice (Case 1, Table 3) was in a boy, aged 8 years, who complained of abdominal pain, vomiting and loss of weight of two weeks duration. When first seen he was subicteric, later he became distinctly although never deeply jaundiced. The temperature was 100. The sharp smooth edge of the enlarged liver was palpable 1½ inches (3.32 cm) below the free border of the ribs, and the total vertical size of the liver, as made out by percussion, was 5 inches (12.7 cm). The spleen was not felt. The urine repeatedly showed only a trace of bile, but a large amount of urobilin. The stool was likewise light in color but never acholic. The case ran a mild ambulant course for about a month and resulted in the patient's complete recovery. The

tetrachlorophenolphthalein test, which was done in the third week of the illness, showed a much more pronounced retention of dye than might have been expected from the very light jaundice or the mild clinical symptoms. The blood serum was a lemon yellow color, indicative of a mild bile retention.

The case of acute yellow atrophy (Case 2, Table 3) occurred in a woman, who was admitted to the surgical department, with a history of

TABLE 3—*Acute Infections or Degenerations of the Liver*

Case No		Mg In-jected per Kg of Body Weight	Percentage of Dye in Blood After		Liver Enlarge-ment	Jaun-dice
			15 Minutes	60 Minutes		
1	Catarrhal jaundice	5	20	25	+	+
2	Acute yellow atrophy of the liver Necropsy	7	30	35	Liver small	(slight) +
3	Nephritis following acute infectious jaundice (Weil's disease)	7	5	2	+	+(fading)

attacks of right sided abdominal pain for a year, aggravation of the pain during the preceding four weeks and jaundice of varying intensity during the preceding two weeks. Examination showed a woman, looking acutely ill, with tenderness on the right side of the abdomen at the level of the umbilicus and a light but definite jaundice. An exploratory operation three days after admission revealed a very small liver and no lesions in the gallbladder or bile ducts. Very thick, dark bile was aspirated from the gallbladder. There was free yellow fluid in the peritoneum. The patient died two days after the operation, and necropsy revealed acute yellow atrophy of the liver. On account of the rarity of such reports since chemical blood examinations have been in use, it is worth recording the examinations of this case.

	Two days before operation	Day before death
Urea Nitrogen	14 mg per 100 c c	14 mg per 100 c c
Nonprotein Nitrogen	31.5 mg per 100 c c	
Uric Acid	1.5 mg per 100 c c	2 mg per 100 c c
Creatinin	1 mg per 100 c c	1 mg per 100 c c
Cholesterol	0.130%	0.07%
Bile	present	present
Sugar		0.130%
Carbon Dioxid		29.8%

The normal sugar and nitrogen (especially the urea) and the low cholesterol are the interesting figures.

The case of infectious jaundice is brought in to show how much more the kidneys were injured than the liver by this general infection. A previously healthy man, aged 36, came in with the typical symptoms

of Weil's disease, with a history of one week's illness with chills, fever, headache, epistaxis and tarry stools. He showed labial herpes, profound jaundice, purpura, ecchymoses, enlarged liver and spleen, and large amounts of albumin and casts in the urine. Examinations of the blood, urine and duodenal contents (unfortunately only in the third week of the disease) for the spirochete of Inada and Ito were negative. The liver function test was not done during the acute febrile stage, as it was felt that a positive result was a foregone conclusion. It was done three weeks after admission, at a time when the patient was convalescent from the acute symptoms and showed only a faint jaundice. The test was normal. At this time the patient showed evidence of a very severe nephritis with extremely high nitrogen retention in the blood, and absolutely no excretion of phenolsulphonephthalein by the kidneys in two hours. (During the acute febrile state, blood chemistry and phenolsulphonephthalein tests had both been normal.) It was evident then that the liver had resumed its normal functions while the permanent damage was to the kidneys.

*Malignant Growths in the Liver*—There were sixteen cases of metastatic malignant tumor of the liver. In this condition the impairment of liver function may be expected to be largely mechanical, and to depend on the extent to which liver tissue is replaced by new growth or is blocked as the result of new growth invading larger bile ducts or blood vessels. Accordingly, the results show considerable variation. Several of the cases were of particular interest.

Case 1 (Table 4) is discussed in detail under the heading General Value of Test 1. Positive value, as it is one of the cases in which the test itself was the first finding to point to serious disease of the liver.

Case 4 (Table 4) likewise presented features of unusual interest. The patient, a previously healthy man, on admittance, had a history of severe right upper quadrant pain for the last three months, not related to eating, with repeated exacerbations and with occasional vomiting. The entire right side of the abdomen was tender. There was a retained right testicle. His temperature ranged from 100 to 102, and there was a moderate leukocytosis. An exploratory laparotomy was done with entirely negative findings. The symptoms subsided and he went home and remained well for about six weeks. Then the same symptoms returned and he was readmitted again acutely ill. This time there was a small, pear shaped mass on deep palpation in the right upper quadrant and the patient was subicteric. The tetrachlorophenolphthalein test showed 12 per cent at fifteen minutes and 7 per cent at one hour—a slight degree of retention. The serum was faintly icteric. An exploratory operation was again done and this time a retroperitoneal cystic tumor was found. The laboratory reported this to be a malignant

embryoma, in all likelihood arising from the retained testicle. The patient did not recover strength after the operation, and at necropsy a number of metastatic nodules were found in the liver.

In sharp contrast to this is another almost identical case (Case 11, Table 4) of embryoma arising from a retained testicle, with numerous

TABLE 4—*New Growths Involving the Liver*

Case No		Mg In- jected per Kg of Body Weight	Percentage of Dye in Blood After		Liver Enlarge- ment	Icterus	Blood Bili- rubin
			15 Minutes	60 Minutes			
1	Biliary fistula after cholecystec- tomy. Subsequent finding of metastatic carcinoma	5	23	25	Indefinite	Sub	Slight icterus
2	Metastatic growths, inoperable, primary growth not found	5	12	12	Huge	?	?
3	Carcinoma probably of gallbladder, very large inoperable tumor	5	12	9	Large	0	Not in- creased
4	Exploratory operation						
4	Retroperitoneal embryoma. Liver metastases. Operation and ne- cropsy	7	12	7	0	0	Sub- icteric
5	Carcinoma of pancreas. Liver metastases. Necropsy	7	18	16	+	+	+
6	Inoperable carcinoma of stomach, huge tumor. No operation or necropsy. Syphilitic	7	5	5	+	0	0
7	Carcinoma of rectum. One nodule in liver at operation. Test four days before operation	7	3	0	0	0	0
8	Carcinoma of stomach. Opera- tion. Liver studded with small growths	7	15	15	+	0	Slightly icteric
9	Metastatic carcinoma. large tumor in liver region, deep but not completely obstructive jaundice	7	20	25	Huge	+	+
10	Recurrent carcinoma of sigmoid. Several nodules in liver at op- eration	5	15	20	0	0	1 200 000
11	Malignant embryoma, retained testicle. Metastases in liver. Ne- cropsy, January 1						
	October 7	7	7	2	+	0	0
	October 29	7	8	2			
	November 30	7	7	2			
12	Colloid carcinoma, hepatic flexure, colon. One large metastatic mass in liver at operation	7	10	10	0	0	0
13	Inoperable carcinoma, sigmoid. Probable liver metastases (diag- nosed only as result of liver function test, not felt at opera- tion)	7	12	7	0	0	0
14	Carcinomatosis, liver metastases. neck gland excised for diagnosis	7		10	Very large nodular	0	1 100,000
15	Metastatic carcinoma peritoneum (papillary adenocarcinoma of ovary). Operation	7		4	0	0	0
16	Carcinomatosis. Large upper ab- dominal tumor (which may not have involved liver). Diagnosis by excision of inguinal gland. No necropsy	7	5	Trace	?	0	0

liver metastases, in which the tetrachlorphenolphthalein test was repeatedly negative. On account of its great importance this case is discussed elsewhere, under the caption Failures of the Test.

On reviewing these cases of metastatic growth of the liver, it is clear that negative findings of the tetrachlorphenolphthalein test do not exclude metastatic nodules. On the other hand it appears that there is



a field of usefulness for the liver function test, in seeking to detect liver metastases before operation in cases of known or suspected carcinoma involving the intestinal tract

*Echinococcus Cyst of the Liver*—There was one case of echinococcus cyst in a woman, aged 42. The patient had been operated on five years before for echinococcus cyst, at which time she says that she had been jaundiced for three months. She had become pregnant three

TABLE 5—*Obstructive Jaundice, All Causes*

Case No		Mg In jeeted per Kg of Body Weight	Percentage of Dye in Blood After		Liver Enlarge-ment	Jaundice	Blood Bilirubin
			15 Minutes	60 Minutes			
Complete Obstruction							
1	Carcinoma of pancreas Operation	10	30	30	+	+	+
2	Carcinoma of pancreas with liver metastases Necropsy	7	18	16	+	+	+
3	Carcinoma of head of pancreas No liver metastases Necropsy	7	20	12	0	+	+
4	Carcinoma of head of pancreas Operation	7	15	20	+	+	+
5	Carcinoma of common bile duct Suppurative cholangitis Necropsy	7	20	25	+	+	+
6	Carcinoma of common bile duct Necropsy	7	20	20	+	+	+
Incomplete Obstruction							
7	Common duct stone cholecystitis Incomplete obstruction four days Operation	5	20	15	+	+	+
8	Previous short attack (from four to eight days) of obstruction due to stone Ducts patent at operation two days after test	5	16	8	0	+	?
9	Recovering from obstructive jaundice of two weeks duration Test twelve days after passage of stone	7	25	25	0	+	1.40 000
10	Ball valve common duct stone, in complete obstruction for nine days (test two days before operation)	7	10	10	0	+	1.70 000
11	Incomplete obstructive jaundice of three weeks duration due to stones and pericholecystitis and pericholangitis Recovery						
	(a) Before operation	5	20	20	+	+	+
	(b) Nine days after operative drainage	7	15	18			
	(c) Twenty five days after drainage	7		7			

months before admission. She vomited constantly for one month before she came to us. At that time she noticed that the epigastrium was swollen. The abdomen was found distended, the entire right side being filled by the smooth, soft liver, the general outline of which was regular. The patient was not icteric but the serum showed increase of bile above normal. Operation revealed that the liver contained a very large number of echinococcus cysts. The tetrachlorophenolphthalein test showed pronounced retention, 15 per cent at fifteen minutes and 15 per cent at the end of one hour.

*Cholecystitis*—Our results in cholecystitis were unsatisfactory and did not lead to any definite conclusions. It is doubtful if the test has any special value in the condition, but the question is being more thoroughly investigated by Dr. Colp on larger surgical material.

*Obstructive Jaundice*—The eleven cases of obstructive jaundice fall naturally into two groups: (a) six cases of total obstruction, all due to cancer involving the common bile duct, and (b) five cases of incomplete obstruction or of convalescence after relief of obstruction, all due to gallstones.

The cases of complete obstruction require little comment. The chief interest in the high retention which they show is the question of why it was not still higher. This will be discussed elsewhere.

The stone cases, however, present several points of considerable importance. In the first place Case 7 (Table 5) shows that an acute, but probably not quite complete obstruction of the common duct by stone, lasting certainly not over four days, can produce decided dye retention (15 per cent at the end of one hour).

Cases 9 and 11 (Table 5) show how unexpectedly slow is the recovery of the dye excreting function after the relief of obstruction. In the former case, probably a complete obstruction of two weeks duration was relieved by spontaneous passage of the stone, but twelve days later the test still showed dye retention of 25 per cent at one hour. The patient made a clinically complete recovery subsequently, but was not tested again. Case 11 (Table 5) is even more instructive. A case of incomplete obstruction of three weeks duration showed one hour dye retention of 20 per cent. Nine days after operative drainage of the common bile duct there was still pronounced retention, and twenty-five days later, though the patient was convalescent and the urine had been free of bile for two weeks and the tissues only showed the faintest residual jaundice, still the dye excretion had not quite returned to normal.

In view of these results, the hope expressed in a previous publication<sup>4</sup> that a prompt return of dye excretion might serve as an indicator of relieved obstruction, will probably have to be abandoned, at least for cases of more than a few days obstruction. It is evident that in obstruction of several weeks duration, even if incomplete, the return of function after the obstruction is gone is unexpectedly slow. Whether this is the result of actual injury of liver parenchyma or of the persistence of cholangitis can only be decided by further study.

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4 Ottenberg, Reuben, and Rosen, Samuel. Possible Application of Phenol-tetrachlorophthalein Test to Obstructive Jaundice, J. A. M. A. **80** 1519 (May 26) 1923.

## CASES OF POSSIBLE FUNCTIONAL IMPAIRMENT OF THE LIVER

*Pneumonia*—Because of the old clinical observation that severe cases of pneumonia often develop jaundice we have tested several cases of pneumonia. The first one was a typical case of lobar pneumonia, involving the entire upper and part of the left lower lobe in a man, aged 40 (Case 1, Table 6). The patient was very toxic and was subicteric in appearance. The liver was enlarged to 3 cm. below the free border of the ribs. The temperature, which had ranged between 103 and 104, dropped to normal and remained there. On the day of the crisis bile was detected in the urine. The first tetrachlorophenolphthalein test was done four days after the crisis, at this time the patient was still slightly icteric, but was in excellent general condition. There was a retention of 11 per cent. at the end of one hour. The test was repeated eight days after the crisis at which time the patient was almost free of

TABLE 6—*Pneumonia*

Case No.		Mg In jected per kg of Body Weight	Percentage of Dye in Blood After		Liver Enlarge- ment	Jaundice	Blood Bili- rubin
			15 Minutes	60 Minutes			
1	Severe lobar pneumonia. Slight jaundice. Four days after crisis.	5	11	11	3 cm.	Slight	Slight
	Eight days after crisis.	6	9	8	3 cm.	Almost gone	Slight
	Eighteen days after crisis.	6	6	2	0	0	0
2	Moderately severe lobar pneumonia. Test immediately after crisis. Subsequent cortical kidney abscess.	7	10	4	0	0	0
3	Right lower lobe pneumonia. Possibly complicating some abdominal condition. No jaundice.	7	10	10	Palpable	0	1 300 000

jaundice. The blood at the end of one hour still showed 8 per cent. of the dye. A third test was done eighteen days after the crisis, there was almost no retention of the dye at the end of one hour. This case, like the cases of obstructive jaundice discussed in the foregoing, suggests that a once injured liver does not rapidly resume its normal function.

The second case (Case 3, Table 6) was one of right lower lobe pneumonia (confirmed by roentgen-ray examination) in a woman, aged 60. It is possible that pneumonia in this case may have been a complication of some undiscovered abdominal condition, most likely cholecystitis, as there was a history of abdominal pain and frequent vomiting for six weeks before admission, and the right upper quadrant of the abdomen was tender. There was no icterus whatever and the blood serum was of a pale straw color. The test showed retention of 10 per cent. of the dye at the end of one hour. The patient left the hospital against our advice, and the case is included only because the most important finding was the lobar pneumonia.

*Myocardial Insufficiency*—On account of the frequent occurrence of enlargement of the liver and of jaundice in cardiac decompensation it was thought worth while to try the test in cases of this kind. The majority of the thirteen cases so tested showed distinct retention of dye. All of these cases showed some enlargement of the liver. It will be noticed that the three cases which showed no retention whatever (Cases 1, 5 and 11, Table 7) were those which showed the least enlargement of the liver. Case 10 (Table 7), a case of calcified pericardium, which showed no distinct retention of the dye, nevertheless showed a very

TABLE 7—*Cardiac Decompensation*

Case No		Mg In- jected per Kg of Body Weight	Percentage of Dye in Blood After		Liver Enlarge- ment	Icterus	Blood Bili- rubin
			15 Minutes	60 Minutes			
1	Coronary Not fibrillating Died	5	6	0	3 cm	0	0
2	Mitral, aortic, tricuspid Necropsy	5	18	18	Huge	Slight	Slight
3	Hypertension Fibrillating Im- proved slightly Went home	6	20	15	10 cm	0	0
4	Emphysema Cardiac decompensa- tion (test repeated after four days) Improved temporarily	5 7	7 10	Trace Trace	4 cm	0	0
5	Hypertension Not fibrillating Subsequently went home entirely compensated	6	5	Trace	3 cm	0	0
6	Mitral and tricuspid Fibrillation Condition fair at time Little improvement	7	11	8	7 cm pulsating	0	Subicteric
7	Mitral, aortic, tricuspid, fibril- lating Went home slightly im- proved	7	10	8	10 cm pulsating	Subicteric	±
8	Atherosclerosis Mitral Anasarca Not fibrillating Died	7	12	12	6 cm	Subicteric	100,000
9	Aortic, mitral, tricuspid stenosis Went home slightly improved	7	28	15	Large, pulsating	Subicteric	80,000
10	Calcified pericardium fibrillating Operation with subsequent relief	7	9	5	Very large	0	150,000
11	Mitral stenosis, aortic and tricus- pid valvular disease Moderate decompensation Discharged im- proved	7	5	3	+	0	0
12	Valvular disease Decompensation Tricuspid Improved	7	20	20	12 cm	0	0
13	Arteriosclerosis Coronary disease Right sided dilatation of heart	7	10	10	14 cm	0	0
14	Suspected bacterial endocarditis Mitral stenosis Tricuspid insuf- ficiency Decompensation	7		7	—	0	0

large liver. This case, however, was one of a very long duration. It will be noticed that with this exception all the cases which showed any trace of icterus showed a marked retention of dye.

In this regard our observations confirm those of Fishberg<sup>5</sup> who showed that the estimation of bile in the blood offered a valuable index as to the degree of cardiac decompensation.

So far as study of our figures goes, the degree of liver impairment has no special relation to prognosis.

5 Fishberg, A. M. Jaundice in Myocardial Insufficiency, J. A. M. A. 80 1516 (May 26) 1923

*Splenic Anemia*—On account of its close, but as yet not very completely understood connection with the hepatic cirrhosis, the findings in splenic anemias are interesting. We had one case. This was in a woman, aged 30, who was admitted because of a large gastric hemorrhage. Ten months before admission she had had an attack of pain in the right side of the abdomen. For two months the abdomen had been enlarged. Examination showed a moderate degree of anemia, a yellowish complexion but no jaundice (blood bilirubin 1:300,000), the liver enlarged to the level of the umbilicus, the spleen enlarged to the brim of the pelvis and within 1 inch (2.5 cm) of the midline. Tests of the urine and feces showed a decided increase in the urobilin. A splenectomy was done and the patient subsequently recovered. At the time of the splenectomy the liver was inspected and appeared normal. The tetrachlorophthalein test was done twice with negative results.

*Hemolytic Icterus*—Of great interest were two cases of acquired hemolytic icterus. The first (Case 1, Table 8), an Italian girl, aged 16,

TABLE 8—*Hemolytic Icterus*

Case No		Mg In- jected per Kg of Body Weight	Percentage of Dye in Blood After		Liver Enlarge- ment	Jaundice	Blood Bili- rubin
			15 Minutes	60 Minutes			
1	Girl, aged 16, jaundice of three years' duration. Spleen very large	7	15	15	9 cm	+	1:15,000
2	Man, aged 24, jaundice of four years' duration	7	8	5	7 cm	+	1:8,000

had noticed the pronounced yellow color of her skin for three years. She was distinctly icteric but well nourished. The spleen and liver were both enlarged to about 3 inches (7.6 cm) below the free border of the ribs. The blood count showed merely slight anemia. The fragility of the red blood cells was normal. Examination of the stools and urine showed a very great increase in the excretion of urobilin. The urine, in addition, contained traces of bile. This patient subsequently had a splenectomy performed and made a complete recovery, losing the jaundice entirely. The pathologic reports on the spleen showed fibrosis, activity of the cells lining the venous sinus and slight atrophic changes in some of the follicles. The tetrachlorophenolphthalein test, done five days prior to the operation showed very pronounced retention.

The second case (Case 2, Table 8), a man, aged 24, had had slowly increasing jaundice for four years. Two years before we saw him an exploratory laparotomy had been done, with entirely negative results. His stools were of normal color and the duodenal tube revealed normal bile flow (the bile contained 17.5 mg of urobilin per hundred cubic centimeters). The urine contained not only bile but urobilin (120 mg

in twenty-four hours) The liver was enlarged to 7 cm below the rib border The red cells showed normal fragility In spite of the jaundice and all the evidences of very active hemolysis, the function test showed only very slight impairment, 8 per cent of dye at fifteen minutes, 5 per cent at one hour

TABLE 9—*Pernicious Anemia*

Case No		Mg In jected per Kg of Body Weight	Percentage of Dye in Blood After		Liver Enlarge- ment	Skin Jaundice	Blood Bili- rubin
			15 Minutes	60 Minutes			
Typical Cases							
1	Woman, aged 49, one year anemia, 24 hours' urine, 30 gm urobilin	7	7	2	0	Lemon yellow	1 15 000
2	Man, aged 30, spleen enlarged	7	4	0	4 cm	0	0
Atypical or Doubtful Cases							
3	Woman, aged 55, weakness or pal- lor ten years Hydrochloric acid present in stomach contents High color index Macrocytosis Smooth tongue	7	9	6	0	Lemon yellow	1 200 000
4	Man, aged 52. Chronic tuberculosis Large spleen and liver 290 gm urobilin in 24 hours' urine, 4.08 gm in 24 hours' stool	7	8	4	+	0	1 90 000

*Pernicious Anemia*—Two cases of pernicious anemia, in spite of the obvious evidence of pronounced hemolysis, showed normal liver function tests or only slight dye retention In addition to these, Case 4 (Table 9) is an unclassified case of grave anemia, in which the striking feature was the great urobilin excretion (279 mg in twenty-four hours urine), and in which nevertheless the tetrachlorphenolphthalein test showed only a suggestion of dye retention Case 3 (Table 9) showed many features of pernicious anemia but the presence of free hydrochloric acid in the gastric contents, and the long course, give reason for some doubt as to the exact classification The dye figures are somewhat higher than in the typical cases

TABLE 10—*Leukemia, Hodgkin's Disease*

Case No		Mg in- jected per Kg of Body Weight	Percentage of Dye in Blood After		Liver Enlarge- ment	Spleen Enlarge- ment	Jaundice	Blood Bili- rubin
			15 Minutes	60 Minutes				
1	Myelogenous leukemia	5	4	Trace	7 cm	To pelvis	0	0
2	Hodgkin's disease (gland excised)	7	4	3	7 cm	+	0	0

*Leukemia and Hodgkin's Disease*—There was one case of each of the above conditions Liver tests were done because it was thought that perhaps it might be possible to detect the liver infiltration which frequently occurs in these diseases Although in both of the cases the liver was greatly enlarged so that it is fair to assume that such infiltration was present, there was no retention of dye This requires explanation and deserves further study

*Control Cases (no liver disease)*—There were twelve control cases, that is, cases in which there was no reason to suspect liver damage. It will be noticed that the results are approximately the same whether the patients received 5 or 7 mg of tetrachlorphenolphthalein per kilogram of body weight. The rather high percentages in Cases 2 and 3 (Table 11) (both receiving 5 mg of dye per kilogram of body weight) were probably due to a little hemolysis of the blood. These were done early in the series, before we realized the importance of avoiding the slightest hemolysis. With the exception of these two cases it can be stated that cases in which there is no liver impairment, uniformly show

TABLE 11—*Control Cases—No Liver Disease*

Case No	Mg Injected per Kg of Body Weight	Percentage of Dye in Blood After		Liver Enlargement	Jaundice	Blood Bilirubin
		15 Minutes	60 Minutes			
1 Pulmonary abscess	5	6	0	0	0	0
2 Pulmonary tuberculosis	5	15	4	0	0	0
3 Ureteral calculus	8	8	5	0	0	0
4 Postencephalitic radiculitis	5	5	0	Palpable	0	0
5 Visceroptosis	5	5	0	Palpable	0	0
6 Diabetic acidosis	7	6	0	0	0	0
7 Chorea	7	7	0	0	0	0
8 Dysentery	7	6	0	0	0	0
9 Cardiospasm	7	7	Trace	0	0	0
10 Inguinal adenitis, diabetes	7	6	2	0	0	300,000
11 Pleurisy with effusion	7	7	2	0	0	400,000
12 Gonorrheal epididymitis	7	5	Faint trace	0	0	0

TABLE 12—*Duodenal Ulcer* \*

Case No	Mg Injected per Kg of Body Weight	Percentage of Dye in Blood After		Liver Enlargement	Icterus	Blood Bilirubin
		15 Minutes	60 Minutes			
1 Duodenal ulcer	5	3	0	0	0	0
2 Duodenal ulcer	7	12	6	0	0	0
3 Duodenal ulcer	7	9	2	0	0	0
4 Duodenal ulcer	6	9	Trace	0	0	0
5 Duodenal ulcer	7	10	5	0	0	0

\* All diagnoses based on clinical findings and roentgen ray confirmation

less than 8 per cent of dye in the fifteen minute sample, and less than 3 per cent of dye in the sample of blood obtained an hour after injection.

Along with this group we wish to present another group of five cases of duodenal ulcer. These were originally intended to form part of the control group.

*Duodenal Ulcer*—It will be noted that four of these cases show rather higher than the usual percentage of dye at fifteen minutes and two of them (Cases 2 and 3, Table 12) show percentages at an hour that are on the verge of retention percentages. We are unable at present to indicate the significance of this. In all the cases the clinical diagnosis

of duodenal ulcer was confirmed by definite roentgen-ray findings but not by operation or necropsy. Possibly further studies, particularly if some slightly more sensitive method of testing can be introduced, may indicate some real connection between liver dysfunction and duodenal ulcer. It is interesting to note that one of our cases of hepatic cirrhosis at necropsy showed a healed duodenal ulcer. Since the etiology of so many cases of cirrhosis is unknown, it is permissible to speculate that chronic infections in the portal drainage area may play a causative role, and that the slight impairment of function noted may have some significance.

#### GENERAL VALUE IN DIAGNOSIS

*Interpretation of the Test as Affected by Jaundice*—Every case that showed distinct jaundice from any cause, excepting pernicious anemia and hemolytic icterus, also showed some dye retention and usually about in proportion to the degree of icterus. It is evident that in obstruction of the bile duct the test is valueless, and in milder degrees of jaundice it is at best only of very limited diagnostic value. Since in a considerable proportion of diseases of the liver, there is more or less jaundice, the tetrachlorophenolphthalein test is limited in its usefulness as a diagnostic measure to those cases of suspected liver disease or dysfunction in which there is no or minimum jaundice. In such cases it may either be of positive value, pointing to the liver as the seat of disease, or of negative value in helping to exclude liver lesions.

*Positive Value of the Test*—As instances of the test's positive value in the following seventeen cases there was distinct dye retention.

It is seen by glancing at the table that the test is most likely to be of diagnostic use (a) in the confirmation of the diagnosis of suspected cirrhosis of the liver; (b) for the detection of liver metastases in cases of malignant disease.

Case 2 (Table 13) in this group is of particular interest because the liver function test enabled us to predict the existence of serious liver lesions, at a time when the other findings of the case did not lead to any suspicion of their presence. The patient was a woman, aged 58, with a history of repeated attacks of severe pain in the right upper abdomen, radiating to the back and shoulder, at intervals over a period of six months. She was very ill, with rigidity and tenderness in the right upper abdominal quadrant and subicteric appearance of the conjunctiva. There was no bile in the urine. Operation showed an acutely inflamed gallbladder with numerous gallstones, cholecystectomy with drainage was performed. A month after operation the patient's general condition was fair but the biliary fistula had not yet closed. At this time the liver function test showed retention of 23 per cent at fifteen minutes and 25 per cent at one hour; the patient's serum was faintly icteric. The cause



of the poor liver function was rather obscure. The patient was allowed to go home, the case being diagnosed as cholecystitis. Three weeks later (two months after the first operation) the patient came back on account of the persistent biliary fistula, and an exploratory laparotomy was done. This time the liver was found to contain many hard nodules of metastatic carcinoma, one of these obstructing the common duct in the hilum was the cause of the persistent fistula.

TABLE 13—*Positive Value of Test in Diagnosis*

Case No		Mg Injected per Kg of Body Weight	Percentage of Dye in Blood After		Liver Enlargement	Icterus	Blood Bilirubin
			15 Minutes	60 Minutes			
1	Atrophic cirrhosis January 5 (subsequent necropsy) January 21 September 21	5	12	12	+	0	0
2	Persistent biliary fistula Metastatic carcinoma Necropsy	5	23	25	0	0	0
3	Hard irregular liver probably metastatic carcinoma No operation	5	12	12	+	0	0
4	Cardiorenal disease Fibrillation Decompensation Mitral insufficiency	6	20	15	10 cm	0	
5	Large carcinoma filling entire upper abdomen on right side Operation	5	12	9	+	0	
6	Probable cholelithiasis (repeated gallstone attacks) No operation	7	12	8	1 cm	0	1 300,000
7	Splenomegaly, cause unknown Possibly early cirrhosis	7	10	8	Large	0	1 400 000
8	Pneumonia Possible cholecystitis	7	10	10	+	0	
9	Portal thrombosis following splenic abscess	9	8	7	+	0	
10	Carcinoma of stomach Liver metastases found at operation	7	15	15	+	Faintly	
11	Atrophic cirrhosis Healed duodenal ulcer Necropsy	7	13	12	+	0	
12	Recurrent carcinoma of colon Liver metastases felt at operation	7	15	20	0	0	1 200 000
13	Atrophic cirrhosis	7	15	15	0	0	
14	Colloid carcinoma of colon One large metastatic mass in liver near the gallbladder	7	10	10	0	0	0
15	Coronary disease Right side of heart dilated	7	10	10	Very large 14 cm	0	0
16	Cholecystitis (typhoid bacillus) and lithiasis Nonobstructing stone in common duct Urine negative for bile	7	10	8	0	0	Faint trace
17	Large carcinoma of sigmoid Test nineteen days after operation when patient was convalescent Liver palpated during operation No masses felt	7	12	10	0	0	0

Case 10 (Table 13) was an instance of a large tumor in the left upper abdomen of a patient, who had been in the hospital for three weeks. It was not noticed that he was jaundiced until the day on which the liver function test was performed. At that time faint jaundice was seen for the first time. Operation showed carcinoma of the stomach with numerous small metastases in the liver.

In Case 17 (Table 13) an emergency operation had to be done for perforation of a large carcinoma of the sigmoid. On account of pei-

tonitis and poor general condition of the patient the liver was only hastily palpated at operation. Nineteen days later the dye test showed marked retention. We believe that it is safe here to infer the existence of liver metastases.

*Negative Value of the Test*—The reserve power of the liver is very large. It is possible for an animal to live on 30 per cent of the normal amount of liver tissue. It is probably because of this that the negative result of a functional test in excluding liver diseases has only limited value. For example, in several of our cases of syphilis of the liver in which large lesions were easily palpable, the function test was quite normal and in these cases the conclusion must be made that not enough liver tissue was involved to show in the test.

TABLE 14—*Negative Value of Test in Diagnosis*

Case No		Mg In jected per Kg of Body Weight	Percentage of Dye in Blood After		Liver En- large- ment	Jaundice	Blood Bili- rubin
			15 Minutes	60 Minutes			
1	Coronary disease, decompensation	5	6	0	Enlarged 3 cm	0	
2	Pancreatic abscess	5	7	Trace	0	0	
3	Pulmonary abscess	5	6	0	0	0	
4	Splenomegaly	5	4	Trace	12 cm	0	0
5	Subphrenic abscess? Pneumonia	6	7	Trace	Palpable	0	0
6	Emphysema. Decompensation (test repeated four days later, pa- tient's condition same)	5 7	7 10	Trace Trace	4 cm	0	0
7	Mycogenous leukemia	5	4	Trace	Very large 7 cm	0	0
8	Hypertension, decompensation, anasarca. Subsequently went home entirely compensated	6	5	Trace	5 cm	0	0
9	Congenital enlargement (angi- oma?) of liver	7	8	Trace	17 cm	0	0
10	Chorea (suspected Wilson's disease)	7	7	0	0	0	
11	Dysentery	7	6	0	0	0	
12	Syphilis of liver Splenomegaly	7	5	Trace	0	0	1 300,000
13	Visceroptosis	5	5	0	+	0	1 200,000
14	Sarcoma of polycystic kidney Operation	7	5	3	0	0	0
15	Syphilis of liver	7	5	Trace	+	0	1 200,000
16	Nephritis following infectious jaun- dice	7	5	2	0	+(fading)	0

On the other hand there were cases in which the question of liver dysfunction or actual liver diseases was raised, and in which a negative finding of the test seemed to be of value and was in agreement with the diagnosis, at which we finally arrived (see Table 14).

Several of these cases were particularly interesting. Thus, Case 2 (Table 14) was a man, aged 42, with a history of several years of epigastric pain and some fever, who, on examination, showed a large, tense rounded mass, the size of a child's head, in the epigastrium. The preoperative diagnosis lay between infected cyst of the liver and a peri-gastric abscess. The liver function test was normal. Operation showed an abscess of the pancreas.

Case 9 (Table 14) was another important case. A stunted, but otherwise well developed boy, aged 8 years, came to the hospital because

of enlarged abdomen, his only symptom or physical sign was an enormously enlarged liver (17 cm, vertical measurement) with a rounded smooth edge. This enlargement of the liver was known to have been present since the age of 1 year. A very complete set of laboratory findings was entirely normal, as was also the tetrachlorophenolphthalein test. While the diagnosis cannot be made with certainty, it seems probable that the condition was a benign tumor, probably an angioma of the liver.

Case 10 (Table 14) was of interest because the liver function test helped to exclude one of the diagnoses which was at first considered namely, Wilson's disease (degeneration of lenticular nucleus with hypertrophic liver cirrhosis). The test was negative and subsequent neurologic study showed the case to be one of chorea.

In Case 11 (Table 14) a chronic dysentery, originating in the Philippine Islands, and probably, though not certainly amebic, the results of the test were interesting in helping to exclude liver abscess. We do not feel, however, in view of Cases 4 and 5 (Table 15), that a negative finding is conclusive. It is interesting to compare this result with the work of Covell,<sup>6</sup> who, using the levulose test for liver function found evidence of marked liver insufficiency in the majority of fifteen cases of dysentery tested.

Case 13 (Table 14) is of interest in the negative sense also, as what appeared to be an unusually large liver had led previous medical attendants of the patient to consider various serious liver diseases, to the great alarm of the patient. The function test was normal, and careful examination of the patient showed that the apparently enlarged liver was not really but only apparently so enlarged, as the result of a general visceroptosis.

In Case 14 (Table 14) the question of the location of a huge upper abdominal tumor was involved. Physical examination did not reveal whether the tumor invaded the liver or not. The tetrachlorophenolphthalein test was negative, and subsequent operation revealed a sarcoma arising in a polycystic kidney and not invading the liver.

*Cases in Which the Test Failed*—There were five cases in which the test might have been said to have failed in the detection of easily demonstrable liver lesions. Of these we set aside three, Cases 1, 2 and 3 (Table 15) of syphilis of the liver in adults past 40. It is interesting to compare the results of these with the positive results in cases of congenital syphilis in young persons, all of which showed pronounced retention. It may be inferred in these older persons that the distortion and nodule formation of the liver was for the most part due to cicatrization as the result of previous gummatous processes, and that the location of the scars was such as not to seriously impair the circulation or bile

drainage of the remaining liver tissue. Probably the long duration of the disease, giving ample time for liver regeneration, was another factor of importance.

In Case 3 (Table 15), however, the gumma was evidently very recent because a large gumma of the dome of the liver broke down, became infected and had to be opened and drained. At operation, the typical syphilitic scarring of the liver was recognized.

Of greater importance, perhaps, are two cases of carcinoma, with liver metastases. Of these, the first is not so very significant because the amount of involvement of the liver was so small. The case (Case 4, Table 15) was one of carcinoma of the rectum. At operation, the surgeon palpated the dome of the liver and found one moderate sized nodule of carcinoma.

TABLE 15—Cases in Which the Test Failed

Case No		Mg In- jected per Kg of Body Weight	Percentage of Dye in Blood After		Liver Enlarge- ment	Jaundice	Blood Bill rubin
			15 Minutes	60 Minutes			
1	Acquired syphilis, man, aged 59 Large, hard irregular liver, large spleen	7 7	5 7	Trace Trace	4 cm	0 0	1 300 000
2	Probable man, kera- titis liver	7	5	Trace	6 cm	0	1 200,000
3	Acquired Infected gumma Deep scars of liver Operation	5	5	Trace	+	0	0
4	Carcinoma of rectum One nodule in liver at operation Test four days before operation	7	3	0	0	0	0
5	Malignant embryoma, retained tes- ticle, numerous liver metastases Operation, November 3 Nec- ropsy, January 1	7 7 7	7 8 7	2 2 2	+	0	0
6	Papillary carcinoma ovary Mil- itary nodules entire peritoneum Large tumor filling upper ab- domen	7		4	0	0	0
7	Carcinomatosis Large upper ab- dominal tumor Diagnosis by excision of an inguinal gland	7	5	Trace	?	0	0

The other case (Case 5, Table 15), however, is one in which there were numerous and large metastases in the liver, and in which the liver function test was persistently normal. It was in a man, aged 58, who had had a laparotomy for a supposed abdominal cyst one year previously, and who for six months had suffered with increasing right sided abdominal pain and progressive emaciation. The right testicle was missing, the liver was enlarged to 7 cm below the rib border. Operation showed an irregular, nodular tumor in the right retroperitoneal region, and the liver studded on all surfaces with hard nodules of varying sizes. The pathologic report was "adenomatous syncytial character suggesting primary testicular tumor." The liver function tests both before and a

month after the operation were quite negative. The patient lived for two months, and necropsy showed that a large part of the liver had been replaced by metastatic tumor.

Two other cases are added (Cases 6 and 7, Table 15) in which liver involvement is likely but not certain. They were both very large cancers filling the entire upper part of the abdomen and it seems improbable that the liver escaped metastases.

On the whole, it is seen that while a positive test definitely shows that there is something wrong with the liver, a negative test does not prove the contrary.

*Comparison of the Tetrachlorophenolphthalein with Other Methods of Testing the Liver Function*—We have made no systematic attempt to compare this test with other liver function tests. In four cases we had a duodenal tube in place while we were doing our test, and we collected the bile by the drop method and noticed the time of the first appearance of the bile. The results were somewhat irregular and did

TABLE 16—*Comparison of Tetrachlorophenolphthalein Test by Blood and Duodenal Methods*

Case No	Mg Injected per Kg of Body Weight	Percentage of Dye in Blood After		Time for First Appearance of Dye in Bile Obtained by Duodenal Tube
		15 Minutes	60 Minutes	
1 Syphilis of liver	7	5	Trace	27 minutes
2 Chronic cholecystitis ?	7	12	8	35 minutes
3 Visceroptosis	7	5	0	13 minutes
4 Splenomegaly	7	4	Trace	40 minutes
	7	3	0	

not correspond at all with the blood findings. This suggests that the duodenal method is less to be relied on than the blood method, which confirms the recent work of Hoxie.<sup>7</sup>

The tetrachlorophenolphthalein test only investigates one, and at that a relatively unimportant, function of the liver. Undoubtedly, in the future, methods based on the more important functions of the liver, such as sugar or fat or hemoglobin metabolism, should become available for clinical use. Unfortunately, none of the many tests of this kind proposed up to the present is sufficiently quantitative or practical to be introduced into clinical medicine. The most promising tests have seemed to be the sugar tests (levulose and lactose) and the phloridzin test, but unfortunately these all introduce the unknown but certainly variable features of intestinal absorption or kidney permeability. For this reason we think that, provided its limitations are clearly recognized, the tetrachlorophenolphthalein test at present is preferable to the others.

<sup>7</sup> HOXIE, G. H. Phenoltetrachlorophthalein Liver Function Test, J. A. M. A. 82: 361 (Feb. 2) 1924.

## SUMMARY AND CONCLUSIONS

In 103 cases, Rosenthal's method has proved a valuable index of liver function. Its use in diagnosis has sharp limitations, it is valueless in cases of obstructive jaundice.

After relief of transient obstruction the ability to excrete the dye returns promptly, but after obstruction lasting more than a week return of function may be delayed for days or weeks.

Slow recovery was also observed after lobar pneumonia (one case).

The test was useful in detecting liver disease in sixteen cases, chiefly cirrhosis, metastatic carcinoma or cardiac decompensation. Its greatest value will probably be in early diagnosis of liver metastases and in early diagnosis of cirrhosis of the liver. It was of service in helping to exclude liver disease in eighteen instances, where findings other than jaundice has suggested that possibility.

There were no false positive results. Two cases of duodenal ulcer showed slight retention. This, together with the fact that one case of cirrhosis at necropsy showed a healed duodenal ulcer, suggests chronic local infections as a possible cause of cirrhosis.

In five cases of proved liver lesions the test failed. Three were cases of hepatic syphilis in adults, one, of a very small cancerous metastasis. One case of extensive liver metastases, in which repeated tests gave negative results, remains unexplained.

A positive test always means serious disability, and in the absence of bile duct obstruction, a serious lesion of the liver. A negative test, however, does not always exclude the presence of serious liver lesions. We regard 5 per cent of the dye in one hour serum as suspicious, and over 8 per cent as conclusive of impaired liver function.

The simplicity of the test, and the fact that absorption from the intestines and excretion by the kidneys are not complicating factors in it, recommend it for clinical use.

# CLINICAL STUDIES ON VENOUS PRESSURE <sup>1</sup>

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AND

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Recent physiologic studies have tended to emphasize the relationship between the pressure of the blood returning to the heart through the veins and cardiac activity. Physiologists may be divided into two schools in this respect at present, one of which, under the influence of certain English workers, especially Starling, believes that it is venous pressure which determines cardiac output at each beat, by influencing the initial length or initial tension of the auricular and ventricular muscle. The "law of the heart," as developed by Starling, establishes a relationship between initial load and energy of contraction in the cardiac muscle as has been shown to exist in skeletal muscle. The other school, led by Yandell Henderson, while recognizing the influence of venous pressure up to a certain point, believes that above this there holds "uniformity of cardiac behavior" in which cardiac output does not necessarily vary with venous pressure but depends on heart rate. The recent review of this literature by Henderson <sup>1</sup> makes it unnecessary to enlarge further on this subject. It may be said that whatever view is taken, the recent increase in physiologic knowledge has greatly improved our conception of the relation of ventricular activity to mechanical conditions in the circulation and has given a real meaning to ventricular incompetence. Ventricular incompetence supervenes when the initial load on the ventricle, represented by the venous pressure, exceeds the physiologic ability of the muscle to respond by increased activity. It is analogous to loading a skeletal muscle beyond the ability of the muscle, under existing conditions, to do efficient work. The muscle fibers stretch beyond their physiologic limits of tonus and fail to contract, or contract inefficiently, to the excessive load. The limit of physiologic response of the normal myocardium is evidently quite wide, as demonstrated by the considerable variation in venous pressure in the normal person under usual activity, the rise of venous pressure during exercise as shown by Hooker,<sup>2</sup> and direct determinations of the relation of venous pressure to cardiac output, as shown in the experimental animal by Meek and Eyster<sup>3</sup>. Indeed it is questioned by some whether it is ever exceeded with a normal heart. The pathologic

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\* From the Department of Clinical Medicine, University of Wisconsin

1 Henderson, Yandell. *Physiological Rev* **3** 165 (April) 1923

2 Hooker, D R. *Am J Physiol* **28** 235, 1911

3 Meek, W J, and Eyster, J A E. *Am J Physiol* **61** 186, 1922

myocardium on the other hand, must be regarded as showing a narrowed range of physiologic response and may thus be more or less easily subjected to a venous pressure beyond this limit. Once the limit is exceeded, a vicious cycle results and with failure of the muscle to respond the blood continues to accumulate in the veins and the load becomes greater until an equilibrium is established. Since the amount of blood supply to the tissues in a unit of time is determined more by activity of skeletal muscle than by any other factor the great importance of absolute muscle rest in cardiac failure, in order to lower the demands on the heart muscle and to reduce to a minimum the return flow of blood through the peripheral veins to the right heart is evident. Restoration of compensation occurs, when, as a result of reduction of the peripheral circulation to a minimum and perhaps myocardial stimulation, the muscle begins to respond with increased work to the load on it. As the muscle becomes more efficient in its contraction the load diminishes, and both cardiac output and venous pressure return within their physiologic limit.

Theoretic considerations such as these would seem to suggest the importance of venous pressure determinations in clinical cases of actual or impending cardiac incompetence. The regulatory load for the right heart is the venous pressure in the systemic veins that of the left heart the venous pressure in the pulmonary veins. The former we can conveniently measure the latter we cannot measure in man at the present time.

#### HISTORICAL

Early descriptions of methods of measuring venous pressure in man, and a few observations on clinical cases were published by Frey,<sup>4</sup> von Basch,<sup>5</sup> Gaertner,<sup>6</sup> Sewall,<sup>7</sup> Oliver<sup>8</sup> and von Recklinghausen.<sup>9</sup> Hooker and Eyster<sup>10</sup> described an instrument, based on von Recklinghausen's method, applicable to clinical work and presented data from the normal and a series of cardiac cases. Determination of venous pressure by the direct insertion of a needle into a superficial vein was made subsequently by Moritz and von Tabora,<sup>11</sup> Schott<sup>12</sup> and others. A graphic method using two arm bands was developed by Frank and Reh.<sup>13</sup>

4 Frey, A. *Deutsch Arch f klin Med* **73** 511, 1902

5 Von Basch, S. *Wien med Presse* **20** 962, 1904

6 Gaertner, G. *Munchen med Wchnschr* **74** 2038, 1904

7 Sewall, Henry. *Experiments on Venous Blood Pressure and its Relations to Arterial Blood Pressure in Man* *J A M A* **47** 1279 (Oct 20) 1906

8 Oliver, G. *J Physiol* **22** 51, 1898

9 Von Recklinghausen, F. *Arch f exper Path u Pharmakol* **55** 463 1906

10 Hooker, D R and Eyster J A E. *Bull Johns Hopkins Hosp* **19** 274, 1908

11 Moritz, F, and von Tabora, D. *Deutsch Arch f klin Med* **98** 475, 1910

12 Schott, E. *Deutsch Arch f klin Med* **108** 537, 1912

13 Frank, L, and Reh, Max. *Ztschr f exper Path u Therap* **10** 241, 1912



These showed a close correspondence to the results obtained by the indirect method of other workers. Hooker, in a series of papers, has studied the normal venous pressure in man and the influence of physical exercise and other factors. Exercise<sup>2</sup> caused an average increase of venous pressure in a vein of the hand of 10 cm of water. The pressure reached 26 and 20, respectively, in two instances. A diurnal variation occurs,<sup>14</sup> characterized by a progressive rise during the day and a progressive fall during the sleeping hours. In this study Hooker<sup>15</sup> was unable to confirm the usually accepted inverse relationship between arterial and venous pressure, as derived mainly from the animal experiments of Plumier,<sup>16</sup> since both arterial and venous pressure fall during sleep. Hooker also made a few observations on surgical patients in bed, and found readings between 3 and 15 cm of water, with a tendency to follow the diurnal variation noted in ambulatory subjects. He further showed that local changes in vascular tonus, produced by warming or cooling the hand while varying markedly the amount of blood in the peripheral veins, did not notably affect the pressure. He concluded that venous pressure is normally independent of peripheral arteriole resistance. In this paper Hooker also described a modification of the original instrument for measuring venous pressure in man. Observations in different age groups by the same author<sup>15</sup> showed a gradual rise from an average of from 8 cm of water in the first decade, to 26 cm of water in the seventh and eighth decades of life. Marked variations were found, however, between different persons in the same age groups, attributed to diurnal variations and the influence of bodily activity.

Clark<sup>17</sup> made frequent venous pressure readings on fourteen patients with cardiac decompensation, and concluded that such determinations had definite value in prognosis and treatment, and gave information as to the degree and progress of the condition not obtainable by other means. He regarded an approximate venous pressure of 20 cm of water as representing the critical clinical level in such cases. Above this level a rising venous pressure has an unfavorable, a falling venous pressure, a favorable prognostic significance. As Hooker<sup>15</sup> notes, this value approximates the normal value found by him in ambulatory subjects of the same age group. Hooker's average for age 50, which was the approximate age of a number of Clark's cases, was 19.04 cm of water. He ascribes this rather anomalous situation to a difference in

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14 Hooker, D. R. *Am J Physiol* **35** 73, 1914.

15 Hooker, D. R. *Am J Physiol* **40** 43 (March) 1916.

16 Plumier. *Arch internat de physiol* **8** 1, 1909.

17 Clark, A. H. A Study of the Diagnostic and Prognostic Significance of Venous Pressure Observations in Cardiac Disease, *Arch Int Med* **16** 587 (Oct) 1915.

the technic of reading the pressures and to the influence of rest in bed remarking that the influence of the latter factor has not been determined. For these reasons he believes his normal figures are not in conflict with Clark's findings in cardiac decompensation.

### METHODS

The instrument used in our clinical determinations was the one originally described by Hooker and Eyster,<sup>10</sup> employing a box covered with rubber-dam and applied to the skin with the aid of glycerin. We prefer this to the later modification of Hooker, in which is used a glass capsule attached to the skin with collodion because, with the former apparatus frequent determinations on different patients can be made with rapidity and ease. Determinations were made at heart level by the technic described in the first paper referred to in the foregoing.

### THE NORMAL VENOUS PRESSURE IN MAN

Preliminary studies were made on several normal subjects carrying on their usual activities throughout a period of twenty-four hours, during which frequent determinations were made. These confirmed

TABLE 1—*Venous Pressure at Bed Rest in Normal Subjects*

Case	Affection	Days of Observation	Total Determinations	Venous Pressures		Average
				Highest	Lowest	
1	Ankle sprain	7	22	+7	-3	-4.7
2	Fractured femur	7	21	+7	+3	+5.4
3	Rest ease	4	11	+7	+3	+4.7
4	Convalescent after acute appendicitis	4	14	+5	+2	+3.2
5	Convalescent after acute appendicitis	3	8	+6	+2	-4.4
6	Chronic sinusitis	2	4	+5	+3	+4.0
7	Rest ease	4	8	+5	+2	-3.0
8	Chronic tonsillitis	2	4	+7	+3	+5.5
9	Interstitial neuritis	2	4	+8	+8	+7.5
10	Rest ease	4	14	+8	+1	+5.0
11	Rest ease	1	2	+5	+3	-4.0
12	Rest ease	1	3	+8	+6	-7.0
13	Convalescent after acute appendicitis	2	9	+7	+2	-4.0
14	Convalescent after acute appendicitis	3	8	+5	+3	+3.7
15	Chronic enteritis	2	5	+5	+4	+4.8
16	Tuberculosis of hip	6	14	+7	-3	+5.0
17	Infantile paralysis	12	20	+8	-2	-5.6
18	Spastic paraplegia	4	9	+10	-3	+5.5
19	Infantile paralysis	15	28	+6	+2	+4.0
20	Infantile paralysis	3	7	+4	+2	+3.4
21	Infantile paralysis	14	29	+6	+2	-4.2
22	Cataract	10	20	+6	+2	-3.8
23	Strabismus	8	16	-6	+2	-4.0

the previous results of Hooker and Eyster<sup>10</sup> that (1) a diurnal variation exists the pressure tending to rise throughout the day and reaching its lowest level before getting out of bed in the morning and (2) that the range of pressures was large. A variation between a few centimeters of positive pressure up to 18 cm. is not uncommon.

From the standpoint of the significance of venous pressure determinations in various clinical conditions on patients ill in bed, it seemed to us of first importance to determine in a considerable group of cases the average bed normal venous pressure and its variations. We therefore started a series of such determinations on patients admitted to the University Hospital for minor surgical conditions or rest treatment. A small proportion of those on whom repeated observations were made, are summarized in Table 1. In addition to those recorded, we have made observations on numerous similar cases and are convinced that the venous pressure in a peripheral vein of a normal subject who is at rest in bed, and who has been in bed for a few hours, rarely if ever rises above 11 cm of water. The highest single reading we have ever obtained in hundreds of determinations was this figure. This reading appears also to be quite independent of age. The older subjects, after ordinary exertion and in the erect or sitting position may, however, show the relatively high reading as found by Hooker<sup>15</sup> in his studies on the influence of age. Venous pressure determinations under conditions of bed rest above 11 cm of water we regard, therefore, as of clinical significance.

#### THE VENOUS PRESSURE IN CARDIAC DECOMPENSATION

Routine determination of venous pressure in cardiac cases with decompensation has been carried out in the University Hospital for several years. These have substantiated the original conclusions of Hooker and Eyster,<sup>10</sup> and the subsequent confirmation by Clark<sup>17</sup> that (1) the peripheral venous pressure rises to an abnormal level in this condition, (2) the degree of rise is approximately proportional to the degree of clinical heart failure, and (3) that such determinations are of value in prognosis and treatment. Further, the work of Clark<sup>17</sup> in demonstrating the relation between venous pressure and urinary secretion in such cases has been confirmed. The urine output in relation to the fluid intake varies approximately inversely as the venous pressure. If venous pressure determinations are made sufficiently frequently, it is usually found that a change in venous pressure precedes the change in urine output. Charts from these cases parallel quite closely those previously published by Clark.<sup>17</sup>

The phase of the subject, which has particularly interested us in a group of these cases, is a possible relation between venous pressure and cardiac size. In six cases of decompensation with subsequent restoration, in addition to frequent venous pressure determinations, we have made teleradiograms at certain intervals. These were made with a bedside roentgen-ray unit, the patient reclining at an angle of 30 degrees on a special back rest, with precautions to secure accurate alinement of the tube and film. The distance from target to film was 2 meters. The

silhouette area and greatest transverse diameter were measured and corrected for distortion. Data from these cases are given in Table 2. The first two cases are of mild decompensation with only moderate elevation of venous pressure. During restoration, the venous pressure fell from 12 to 8 cm. in the first and from 10 to 5 cm. in the second. No definite changes occurred in area or transverse diameter of the cardiac silhouette. The remaining cases were of more severe decompensation with much higher initial venous pressure. Case 3 showed a total reduction of 17 per cent in area, and 3 per cent in transverse

TABLE 2—*Venous Pressure and Heart Size in Cardiac Decompensation*

Case	Disease	Days of Hospital	Water Intake in Ounces	Urine Output in Ounces	Venous Pressure in Cm of Water	Telerradiogram		Change in per Cent of Preceding Determination	
						Area in Sq Cm	Transverse Diameter in Mm	In Area	In Tr Diameter
1	Mitral stenosis, mitral regurgitation, auricular fibrillation	1	14	33	12	202	163		
		2	20	30	11	206	160	+ 2	- 2
		5	30	35	10	206	160	0	0
		8	30	31	6	209	160	- 2	0
		9			8	195	161	- 5	- 1
2	Mitral stenosis mitral regurgitation	2	40	25	10	185	159		
		3	55	30	7	187	153	+ 1	- 4
		5	35	35	5	183	160	- 2	- 4
3	Mitral regurgitation, mitral stenosis, auricular fibrillation	1	42	6	23	304	200		
		6	52	19	14	268	190	-11	- 5
		15	38	19	18	265	190	- 2	0
		25	28	28	8	256	193	- 4	- 2
4	Mitral stenosis	2	35	10	23	190	136		
		6	37	22	13	193	141	- 2	+ 4
		13	30	32	9	170	126	-12	-11
5	Mitral regurgitation	1			24	227	188		
		2	46	4	17	217	186	- 4 5	- 1
		3	31	18	15	221	185	+ 2	0
		4	38	68	12	211	178	- 5	- 4
		5	36	44	9	217	180	+ 3	- 1
		10	37	36	10	211	167	- 3	- 7
6	Mitral stenosis Mitral regurgitation Auricular fibrillation	1	33	7	23	221	164		
		3	40	20	20	222	171	0	- 4
		6	45	12	13	227	172	- 3	+ 1
		15	30	35	7	218	163	- 4	- 5
		40	37	37	7	229	169	+ 5	+ 2
		55	30	17	17	238	173	+ 4	- 3
		57	25	25	8	210	157	-12	- 9

diameter. Corresponding figures in Case 4 were 10 per cent reduction in area and 7 per cent decrease in diameter and in Case 5, 7.5 per cent decrease in area and 11 per cent decrease in diameter. In Case 6 there were two well marked periods of decompensation as determined clinically. In the first, the venous pressure fell from 23 to 7 cm. There was an apparent increase in area of 4 per cent and an increase in diameter of 2 per cent. In the second period of decompensation the venous pressure fell from 17 to 8 cm. There was a reduction of 12 per cent in area and 9 per cent in diameter. No data are at present available to determine with certainty the error of determinations of this type on bed patients. The changes in the area observed are relatively small

but reach considerable magnitude if calculated as heart volume<sup>18</sup> The influence of falling heart rate as compensation is reestablished, would presumably act in the opposite direction to that found, namely to increase the heart size, but here again available data are not entirely satisfactory (Heitler<sup>19</sup>) A single observation which we have made on a case of paroxysmal fibrillation, not associated with evidence of decompensation, showed a reduction in the orthodiagraphic area amounting to 16 per cent during the attack when the cardiac rate was 108, as compared with a normal rate of 84 Return to normal area occurred on the cessation of the attack, the two areas agreeing within 3 per cent The transverse diameter was reduced 12 per cent during the attack, returning to within 2 per cent of the previous transverse diameter Venous pressure before and subsequent to the attack was 8 cm, during the attack, 9 cm of water

We feel that our results indicate that, as the decompensated heart regains compensation, there is a tendency toward reduction of its size, which parallels approximately the falling venous pressure

#### COMPENSATED CHRONIC CARDIAC DISEASES

We have made a number of observations on cases with chronic cardiac disease at bed rest for some condition other than cardiac If these cases are clinically well compensated, venous pressure determinations are within the normal range Cases showing clinical evidence of rather poor compensation may show pressures in the upper limits of normal, with an average above the usual normal case

#### ACUTE RHEUMATIC FEVER

Repeated venous pressure determinations on patients with this disease throughout their stay in the hospital, failed to reveal in any instance a reading above the normal bed maximum, and the average determinations were approximately normal Observations on these cases we regarded as of especial interest, because of the definite cardiovascular findings almost uniformly present and because of the frequency of the development of valve lesions This interest led us to extend our observations to a series of cases in which, in addition to venous pressure observations, there were also carried out careful and frequent clinical examinations, determinations of gross alterations in the peripheral circulation and a study of capillary flow and pressure The capillary observations were made with the apparatus and method of Danzer and Hooker<sup>20</sup> Our first effort was to establish a series of normal observa-

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18 A change of 17 per cent in area, according to Bardeen's (*Am J Anat* 23 423 [March] 1918) determinations in the human heart would represent a change of approximately 24 per cent in volume

19 Heitler, M *Berlin Wchnschr* 48 281, 1906

20 Danzer, C S, and Hooker, D R *Am J Physiol* 52 136 (May) 1920

tions under the conditions of our clinical studies. Observations were first made on twenty normal subjects in the sitting position. These subjects were between 17 and 26 years of age. Thirteen were men, seven were women. A series of pressure readings was made in each case and the average obtained. In addition to pressure readings, the number of capillary loops in a microscopic field through which blood flow was evident was stated in percentage of the total number of loops visible in the field. This figure is given as the percentage of patency. The average capillary pressure in the group was 21.85 mm. of mercury, which approximates the figure of 22.2 mm., found by Danzer and Hooker in thirty-one subjects. The highest average reading obtained in any subject was 28.5 mm., the lowest 19 mm. The usual field under the microscope showed from 12 to 14 capillary loops in the distal row, with a patency of about 75 per cent., in other words, blood flow was present in about three-quarters of all capillary loops visible. This varied from 50 to 90 per cent. in the different subjects. The venous pressure in these subjects varied between 7 and 14 cm. of water, with an average of approximately 11 cm. No definite correspondence between capillary pressure and venous pressure within these ranges could be established. In the venous pressure readings below the average for the group the capillary pressure averaged 21.1 mm., in those above the average, the capillary pressure averaged 21.6 mm. Danzer and Hooker note the relative constancy of capillary pressure and the absence of any marked diurnal variation. This is in contrast to venous pressure, which is quite variable through wide limits in subjects under ordinary conditions of life and shows a definite diurnal variation.

Danzer and Hooker note a fall of capillary pressure in two cases in the recumbent position, and state that in hospital bed cases, readings between 13 and 15 mm. are the rule. In extending our own observations to provide a normal basis for our clinical studies, we carried out observations on five patients confined to bed for bone fractures and showing no cardiovascular pathologic changes. The highest average pressure found in these cases was 17.5 mm., the lowest 14 mm., with an average for the five of 15.6 mm. Flow through visible loops comprised approximately the same percentage as in the series of subjects in the erect position.

The studies carried out on ten patients with acute rheumatic fever are summarized in Table 3. All of these were students in the University who had had a physical examination on entrance. Only one showed evidence of cardiac involvement before the onset of the acute rheumatism. Evidences of low vasomotor tonus manifested by these patients were low diastolic pressure, high pulse pressure, macroscopic capillary pulse and auscultatory sounds over the peripheral arteries. Venous pressure observations showed no change from the normal. Capillary

TABLE 3—*Acute Rheumatic Fever*

Pre-vious At- tacks	Pre-vious Cardiac Find- ings	Dur- ation of Ob- serva- tion	Cardiac Findings										Arterial Pressure			Venous Pressure			Capillary Observation			Fe- moral Shot Sound	Cyano- sis Nail Bed		
			Basal Sys- tolic	Apical Sys- tolic	P-e Sys- tolic	Dis- tolic	Pulmonic Per- cussion	Accen- tuated to	Sys- tolic	Dis- tolic	Pulse	Hgh	Low	Aver- age	Average Pres- sure	Patency	Pulsa- tion	Flow*							
1	1	None	29				P	P	P	P	113	57	56	3	6	4	9	100	N	N	P	P	P	P	
2	1	Aortic and mitral	102	P							127	60	56	7	5	6	25	100	P	N				P	
3	1	None	43		P						125	64	61	8	5	6	19	50	Red	Red				P	
4	0	None	31		P						113	64	49	5	3	4	12	50	N	N				P	
5	0	None	22								110	65	15	5	3	4	9	100	N	N				P	
6	1	None	15					P			105	65	40	8	4	6	11	100	N	N				P	
7	0	None	19		P						135	70	65	8	3	6	13	90	Red	Red				P	
8	0	None	23		P			P			118	74	44	8	3	5	12	50	N	N				P	
9	0	None	80		P			P			116	52	34	8	3	6	13	75	N	N				P	
10	0	None	20		P			P			116	58	58	7	3	4	13	75	N	N				P	
Average				60	80	10	20	80	20	118	66	58	6.7	3.9	5.1	13.6	85	---	---	---	---	---	---	---	90

\* P, indicates present, N, normal, Red, reduced

pressures averaged slightly but definitely lower than the control series of normal bed patients. If the one case of definite organic valvular disease is excluded (Case 2), this difference is more marked. The average patency of observed capillaries was somewhat higher than normal. Capillary flow appeared normal in all but two, where it was slightly reduced. Acute rheumatic fever appears to be associated, therefore, with a reduction in the peripheral tonus of the blood vessels in a very high percentage of cases. Venous pressure is unaltered, however, and this fact further supports the conclusion that changes in venous pressure are due much more to retrograde influences from the heart than to alterations in peripheral resistance.

#### LOBAR PNEUMONIA

The frequency with which cardiac failure supervenes in lobar pneumonia is well known. Whether this failure is usually due to primary overload of the right heart as a result of conditions in the pulmonary circuit or whether it is primarily myocardial with a toxic basis has been the subject of much discussion. In either event the hemodynamic conditions at the time of failure should be similar, and the event should be signalled by or at least associated with a rise of venous pressure. Levy,<sup>21</sup> in a series of twenty-one cases of lobar pneumonia, found tele-radiographic evidence of cardiac dilatation in 62 per cent. He interpreted this as indicating an increased load on the heart with dilatation and increased work. None of these cases showed clinical evidence of cardiac failure. Venous pressures were not measured as a routine, nor are figures given, but the statement is made that in a number of cases venous pressure was normal.

We have made frequent venous pressure observations in eight cases of lobar pneumonia. In six of these the venous pressure was well within the normal range throughout. These cases showed no clinical evidence of cardiac failure. In two cases, periods of cardiac failure supervened and in each were associated with an abnormally high venous pressure. In one case two definite periods of clinical decompensation occurred with ultimate recovery. Parallel observations of capillary flow and cardiac size were made in this case, and the data would seem to be of sufficient interest to present in some detail.

#### REPORT OF CASE

*History*—Mrs. K., aged 53, had a chill thirty-six hours previous to hospital admittance. There were signs of consolidation of the left lower lobe, and a systolic murmur at the apex. Blood pressure, systolic 108, diastolic 68, venous pressure 8. Capillary circulation in finger nail bed was normal. The pulse

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<sup>21</sup> Levy, R. L. The Size of the Heart in Pneumonia, *Arch. Int. Med.* 32: 359 (Sept.) 1923.



was 120 On the second morning in hospital the patient became much more toxic and dyspneic Leukocytes, 16,000 These was extension of consolidation to whole left lower lobe The venous pressure was 9 in the morning, 13 at 7 30 p m The capillaries showed contraction but no signs of stasis Pulse, 120 The heart sounds were good Pulmonic second sound was accentuated Systolic pressure, 116, diastolic, 58 At 11 p m large numbers of moist râles were heard over the chest Involvement of the right lower lobe was present Capillaries showed definite evidence of stasis At 6 o'clock the next morning (third day in hospital) the patient was very cyanotic and ashen The pulse was 116 There was no enlargement of the heart to percussion Accentuation of P<sup>2</sup> less Stasis in more than one-half the capillary loops observed, slow streaming in others, and general dilatation of capillaries The venous pressure was 17 Systolic pressure 118, diastolic 66 Two hours later there was marked increase noted in the extent of pulmonary edema Marked dyspnea was present Oxygen, strophanthin (intramuscular) and camphorated oil (intramuscular) were administered The next morning (fourth day in hospital) the cyanosis was lessened There was no important change in the pulmonary signs Large and medium moist râles in great numbers were still present throughout both chests There was no enlargement of the heart to percussion P<sup>2</sup> was somewhat accentuated The venous pressure was 14 Subcyanosis was present in contrast to the deep cyanosis and ashy gray of yesterday The pulse was of better quality, rate 112 Systolic pressure 120, diastolic 64 In the afternoon of the same day the condition was similar The venous pressure was 13 Stasis in the capillaries was definitely less On the next morning (fifth day in hospital) there was a great reduction in the number of large bubbling and other moist râles There was no extension of consolidation Cyanosis was much less marked The dyspnea was much lessened Pulse 116, systolic pressure 124, diastolic 70 Signs of stasis in capillaries were much less marked The streaming of blood was much faster and there was practically no beaded flow The venous pressure was 7 In the afternoon of this day the venous pressure was 9, systolic pressure 128, diastolic pressure 74 There were no large bubbling râles The medium moist râles were lessened, and there was marked subjective improvement Pulse rate, 120 On the next morning (sixth day in hospital) the condition was unchanged Resolution was beginning in the lower lobes Venous pressure 9, systolic pressure 128, diastolic pressure 64 Capillaries showed increased stasis Venous pressure in the afternoon, 8 Reduction in degree of capillary stasis On the next morning (seventh day) signs of resolution were marked at bases but lower portion of the right upper lobe was now involved The pulse rate was 130, systolic pressure 132, diastolic 70 Venous pressure, 14 Increase of cyanosis Intramuscular strophanthin again employed, with increase in capillary stasis with beaded flow In the afternoon the pulse rate was 120, systolic pressure 130, diastolic 68, venous pressure 14 Signs of stasis in the capillaries were lessened Pulmonic second sound was accentuated At 10 30 p m venous pressure was 10 cm, systolic pressure 116, diastolic pressure 58 Only very slight evidence of stasis was present in the capillaries Definite improvement was noted in the general condition on the following day (ninth day in hospital) The lungs were clearing throughout The first heart sound was of excellent quality, the systolic murmur was louder Pulse rate 96, systolic pressure 110, diastolic 56, venous pressure 4 cm There was very little, if any, sign of capillary stasis Subsequent to the ninth day the gradual improvement continued to the twenty-sixth day, with no further signs of circulatory embarrassment Twice daily observations of venous pressure gave readings varying between 3 and 7 cm A walled off empyema sac in the left axilla was drained on the eleventh day, under ether anesthesia No rise of venous pressure developed Improvement following this time was more rapid and the patient was discharged from the hospital on the fifty-fourth day Frequent observations of the capillaries showed a normal flow throughout this period

During the first five days the temperature ranged between 100.8 and 102 It then began a fall by lysis, and the first normal temperature (98.6) occurred on the sixth day An upward trend in the temperature then began, continuing until

a second gradual decline on the eighth day. The leukocytes rose to a maximum of 29,000 on the sixth day, and then gradually declined. Fluids were taken in rather large quantities from the start, reaching a maximum of 122 ounces (236 cc) on the third day. Urine output was much below fluid intake until the eighth day, and subsequently the two ran approximately parallel with the urine somewhat below fluid intake. During the period of pulmonary edema and circulatory embarrassment there was thus definite fluid retention, with subsequent fluid loss as the condition of the circulation improved.

Teleradiograms for the heart size were made on the sixth, seventh, ninth, twenty-first and twenty-seventh days. Unfortunately, these do not include the first period of cardiac failure and high venous pressure, but they do include the second period of less marked decompensation extending through from the seventh to the ninth day inclusive. The five teleradiograms varied in area from 114 to 122 sq cm, the transverse diameter varied between 129 and 133 mm. These variations may be considered as falling well within errors of teleradiographic technic and to have no significance. Changes in the shape of the heart were also insignificant, the different teleradiograms being practically superimposable.

The stasis in the capillaries and rising venous pressure in this case, preceding the definite clinical evidence of cardiac embarrassment are particularly interesting. The absence of demonstrable changes in cardiac size paralleling the marked variations in venous pressure, as determined by percussion during the first period and teleradiograms during the second period of cardiac decompensation, is evidence of the importance of other factors which influence heart size, such as variations in tonus of the muscle and probably changes in the rate of beat. It seems evident that a knowledge of the course of venous pressure during pneumonia is more important as indicative of impending or present cardiac failure than efforts to determine heart size by percussion or even by more accurate roentgen-ray methods.

#### THE EFFECT OF VENESECTION ON VENOUS PRESSURE

It has been shown by Meek and Eyster<sup>22</sup> in the experimental animal, and by us<sup>23</sup> in normal man, that hemorrhage or infusion not greater than 10 per cent of the total blood volume has only a transitory effect on venous pressure. Quite different, however, is the effect of venesection on the abnormally high venous pressure in cardiac insufficiency. Under such conditions the venous pressure may rapidly fall and remain within normal limits for prolonged periods. In one case under our observation a venous pressure of 22 cm was reduced to 5 cm, gradually rising to 10 cm in the course of the next six hours. In another, venous pressure was reduced from 18 cm to 6 cm remaining subsequently within the normal range. A normal venous pressure thus tends to be maintained, while an abnormal venous pressure tends to fall to the

<sup>22</sup> Meek, W. J., and Eyster, J. A. E. *Am J Physiol* **56** 1 (May) 1921  
 ibid **61** 186 (June) 1922

<sup>23</sup> Eyster, J. A. E., and Middleton, W. S. *Am J Physiol* **68** 581 (May) 1924

normal range after moderate hemorrhage. Observations made in cardiac disease indicate that the general blood volume is not increased (Keith, Rowntree and Geraghty<sup>24</sup>). Increased vasoconstriction must be a universal accompaniment of decompensation, since as is well known in this condition that in spite of diminished cardiac output arterial blood pressures are normal or higher than normal. This vasoconstriction is probably an effort to maintain a normal capillary pressure in the tissue in the presence of a reduced cardiac output. It places, however, the necessity for greater work on the ventricles and if they fail to meet this, a further rise of venous pressure results. The heart is in the condition of a skeletal muscle with a load so great that its contractions are small and inefficient. While the total blood volume may not be increased, evidently the proportionate blood volume in the veins is increased. If now the initial load is reduced by withdrawal of blood from the veins and venous cisterns to a point where the muscle can respond with efficient contractions and if the muscle is still in condition to respond, an immediate increase in stroke volume occurs. With increased output into the arterial system, relaxation of the vasoconstrictor center comes, and the amount of work that the heart has to do is diminished. The heart is now in the condition in which the work demanded is reduced and its initial load, namely, the venous pressure, is within the physiologic limit of response of the muscle. The "vicious circle" of cardiac decompensation is broken, and a return made toward normal circulatory conditions.

The rational basis for venesection in cardiac decompensation we believed therefore to be a high and rising venous pressure. We regard it as a most important therapeutic procedure and one too often delayed until the cardiac muscle is no longer able to respond favorably to a decrease of its initial load.

#### VENOUS PRESSURE IN DISEASES OTHER THAN CARDIOVASCULAR

Numerous observations on bed patients, with various diseases not involving the cardiovascular system, have failed to reveal any noteworthy departure from normal bed patients. Acute infections with febrile reactions and dilatation of skin vessels may show marked variations in the degree of filling of the peripheral veins, but without change in venous pressure, an observation that coincides with Hooker's<sup>14</sup> observations that vasomotor changes, induced in the healthy subject, may affect the amount of blood in the veins but not the venous pressure. Marked increase in peripheral blood velocity, which must be present in

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24 Keith, N. M., Rowntree, L. G., and Geraghty, J. T. A Method for the Determination of Plasma and Blood Volume, *Arch. Int. Med.* **16**: 547 (Oct.) 1915.

advanced primary anemia, likewise causes no noticeable change in venous pressure. Our venous pressure observations in this condition include one case studied in detail from the hemodynamic aspects by Fahr and Ronzone<sup>25</sup>. In this case it was shown that the viscosity of the blood was lowered to 45 per cent of its normal value, that many of the skin capillaries were constricted, thus shunting the main mass of blood through the vital organs and that cardiac output was increased to about two and a half times the normal value. In twenty-three venous pressure observations on this case, extending over a period of fourteen days, the highest reading was 8 cm, the lowest 4 cm, with an average of 6.2 cm. These observations support the general conclusion that peripheral venous pressure in man at rest in bed is largely independent of factors affecting the flow of blood in the peripheral vascular system so long as the heart is competent. Changes in peripheral resistance through vasomotor influences or alterations in blood viscosity tend, of course, to vary the amount of blood passing into the larger veins, and this factor alone would undoubtedly cause variations in venous pressure were it not for the well adjusted response of the heart muscle to the venous load. Lack of physiologic response on the part of the heart muscle we believe to be the one factor which is responsible for the occurrence of an abnormal venous pressure for more than perhaps a brief interval. The important conclusion follows, that a sustained venous pressure above the normal level means invariably a failing heart muscle.

Local causes for abnormally high venous pressure in certain peripheral veins may occasionally be encountered. Marked edema of the hands and forearms may in a few cases make determination impossible. Phlebosclerosis was mentioned by Hooker and Eyster<sup>10</sup> as an occasional cause of abnormally high readings, but such cases are undoubtedly rare. We have had no such instances in our present work. Local pressure on the large veins from any cause may occasionally produce high local venous pressures, but such instances are usually evident. We have had one very interesting case of Hodgkin's disease, with extensive involvement of the mediastinum, in which there was a progressive rise of venous pressure in the veins of the upper extremity as the disease progressed. This patient was observed from the early inception of the disease until death. During a period of over nine months, frequent venous pressure observations were made. There was a rise from an average of below 8 cm in the early stages, to approximately 20 cm just before death. Venous pressure in the veins of the leg was normal throughout. Necropsy showed very extensive involvement of the

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25 Fahr, George, and Ronzone, Ethel. Circulatory Compensation for Difficult Oxygen Carrying Capacity of the Blood in Severe Anemias, *Arch Int Med* 29: 331 (March) 1922.

mediastinum, with inclusion and partial obliteration of the superior vena cava. In a case of aortic aneurism,<sup>26</sup> venous pressure readings were approximately twice as high in the veins of the left hand as in the right hand.

#### SUMMARY AND CONCLUSIONS

The venous pressure in the peripheral veins of normal man, in a condition of bed rest in the prone position, rarely if ever rises above 11 cm of water. Its actual height under rest conditions is largely independent of age. Readings above this level, if rare causes of local obstruction are excluded, invariably mean cardiac decompensation in our experience. Marked changes in venous pressure under such conditions are apparently accompanied by corresponding changes in the volume of the heart, as determined by roentgen-ray methods. Similar changes in venous pressure accompany cardiac decompensation in pneumonia, as well as the usual decompensation from primary cardiac disease. While the normal venous pressure is affected only temporarily and within small range by moderate withdrawal of blood, the abnormal venous pressure in cardiac decompensation may show a much greater and more lasting reduction. Venous pressure changes in cardiac decompensation usually definitely precede changes in fluid equilibrium of the body and the general clinical condition. We believe, therefore, that routine determinations of venous pressure in cardiac decompensation and pneumonia offer a most valuable aid in following the course of the condition and as a guide to rational therapy.

Changes in the peripheral vascular system, associated with alterations in capillary pressure and flow, alter the venous pressure in the larger veins little if at all. Venous pressure is a measure of the initial load on the right heart and depends primarily on, and is an indication of, cardiac behavior. Observations on cases of acute rheumatic fever show normal venous pressures in the presence of extensive changes in the peripheral circulation and the clinical development of valve lesions. As is well known in such cases cardiac failure rarely if ever supervenes in the acute phase.

The main conclusion to be derived from this work is that, excluding local causes of venous obstruction, abnormal venous pressures invariably mean cardiac failure, independent of the cause of failure or the associated disease.

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26 Middleton, W. S. *WIS. M. J.* 21:189 (Oct.) 1922.

# THE REGULATION OF RENAL ACTIVITY <

## IX THE EFFECT OF UNILATERAL NEPHRECTOMY ON THE FUNCTION AND STRUCTURE OF THE REMAINING KIDNEY

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In the preceding paper of this series it was shown that a certain functional measurement (the ratio  $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c c of blood}}$ ) varied in direct proportion to the weight of normal renal tissue<sup>1</sup> If that is so, the removal of approximately 50 per cent of the renal tissue of the body by means of a unilateral nephrectomy should lead to a 50 per cent decrease in function But since the conditions required for this particular functional measurement cannot be fulfilled immediately after an operation, and since unilateral nephrectomy is at once followed by a progressive increase in the size of certain parts of the secreting elements of the remaining kidney, it follows that the nephrectomy experiments which we report in this paper do not have that simplicity which was attained in the direct comparison of total renal weight and function On the other hand, the specialized nature of the concomitant structural changes give them an added interest

Under ordinary conditions unilateral nephrectomy has no effect on renal function, or rather it has no appreciable effect on such measurements as are customarily regarded as being indices of renal functional capacity Thus Rosenstein<sup>2</sup> (1871), found that there was no decrease in the rate of urea excretion even on the first day after the operation Ribbert<sup>3</sup> (1896) was unable to detect any disturbance in the secretion of urine, although he found that there was some delay in the excretion of large amounts of carmin Sacerdotti<sup>4</sup> (1896) found that the volume of urine and the rate of urea excretion was not appreciably affected, and he attributed the decrease in urine volume found by Tuffier<sup>5</sup> (1889) to the effect of the anesthetic and the shock of the operation Maugeris<sup>6</sup> (1908), found that the volume of urine was normal in from three to

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1 Taylor, F B , Drury, D R , and Addis, T Am J Physiol 65 55 (June) 1923

2 Rosenstein Virchows Arch f path Anat 53 141, 1871

3 Ribbert Bibliot Med 100 16, 1896

4 Sacerdotti Virchows Arch f path Anat 146 267, 1896

5 Tuffier Etudes experimentales sur la chirurgie du rein, Paris, 1889

6 Maugeris These de Paris, 1908

four days after operation and Ferron<sup>7</sup> (1910), in experiments on twenty-three rabbits found no evidence of abnormality in urea or chlorid excretion. Schilling<sup>8</sup> (1905) noted no constant change in the volume of urine in rabbits after nephrectomy, but in a few experiments he found that soon after the operation the concentration of chlorid in the urine was lower than usual when large amounts of sodium chlorid were given and water was restricted. He also found that there was a delay in the increase in the volume of urine after the intravenous injection of salt solution. Ambard and Papin<sup>9</sup> (1909) showed that unilateral nephrectomy did not impair the urea concentrating capacity of the remaining kidney. Hohlweg<sup>10</sup> (1915) found a slight increase in the nonprotein nitrogen concentration in the blood some days after the removal of one kidney. Karsner, Bunker, and Grabfield<sup>11</sup> (1915) noted a slight increase in the nonprotein nitrogen of the blood in one dog, but none in the second. In both animals the excretion of nitrogen in the urine was decreased, but in a third dog, from which 66 per cent of the total renal tissue had been removed, the nitrogen excretion was somewhat increased. Rowntree and Geraghty<sup>12</sup> (1912) in the course of a study of the rate of excretion of phenolsulphonephthalein, tied the vessels of one kidney while the dye was being excreted. They did not always find a decrease in the rate of excretion and when it did occur it was of slight degree. Addis and Watanabe<sup>13</sup> (1916) found that there was an increase in the volume of urine, in the rate of urea excretion, and in the concentration of urea in the urine and in the blood after tying one ureter.

There is thus a general agreement that no obvious functional defect is necessarily produced by removing one kidney. This fact is often cited as an illustration of the reserve power of the renal tissue. It is also quoted as an indication of the futility of seeking for any relation between renal structure and function. It is partially responsible for the fact that, for the most part, clinical investigators have given up the attempt to reach any conclusions in regard to the amount of normally functioning tissue remaining in the kidneys of individuals suffering from "Bright's disease." But it is axiomatic that a quantitative relation between structure and function exists, and it would seem almost certain that under some conditions and with some methods this relationship

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7 Ferron. These Bordeaux, 1910.

8 Schilling. Arch f exper Path u Pharmacol **52** 140, 1905.

9 Ambard and Papin. Arch internat de physiol **8** 437, 1909.

10 Hohlweg. Mitt a d Grenzgeb d Med u Chir **28** 459, 1915.

11 Karsner, Bunker and Grabfield. J Exper Med **22** 544, 1915.

12 Rowntree, L. G., and Geraghty, J. T. An Experimental and Clinical Study of Phenolsulphonephthalein in Relation to Renal Function in Health and Disease, Arch Int Med **9** 284 (March) 1912.

13 Addis, T., and Watanabe, C. K. J Biol Chem **28** 251 (Dec) 1916.

should be demonstrable. From the experiments we have cited it must be concluded that the particular conditions and methods employed are valueless for the purpose of determining the amount of functioning tissue, and since any other aim of functional measurements is, in our view, of very doubtful value in clinical work, the whole of experience derived from this more than fifty years of work constitutes an indictment of the clinician's functional methods, a criticism which in part at least may explain the notorious lack of concordance between the expectations of the physician and the results of the pathologist, in regard to the amount of structural change in the kidney in "Bright's disease."

The theory of the coordination of renal structure and function was outlined in 1917,<sup>14</sup> and a test which embodied these principles was recently described.<sup>15</sup> But it should be noted that in 1905 Schilling<sup>8</sup> complied with one of the necessary conditions, the imposition of strain, and was able to show that the increase in the volume of urine, which follows the injection of large amounts of saline solution, was delayed after unilateral nephrectomy. And Addis and Watanabe<sup>13</sup> had found that the ratio  $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c.c. of blood}}$  was lowered in rabbits with one kidney when large amounts of urea were given, although the other essential condition, the exclusion of various extrarenal factors which accelerate or inhibit renal activity, was not adequately dealt with in their experiments. In man it is possible to neutralize these extrarenal factors,<sup>16</sup> but in animals the fact that the stomach tube must be used and that the bladder has to be catheterized, induces conditions under which their varying effect becomes noticeable, so that the urea ratio in individual rabbits never becomes constant. In a group of animals, however, these fluctuations tend to counterbalance one another, and the average ratio may be expected to give a close approximation to the amount of secreting tissue. But our primary object in these experiments was to determine whether such relatively simple methods as measurements of the rate of water and urea excretion, or of the concentration of urea in the urine or in the blood, might enable us to follow the structural alterations which follow unilateral nephrectomy, if pains were taken to carry out these observations under the conditions which are best adapted for revealing the underlying relation between structure and function.

#### METHODS

Rabbits of from 2,300 to 2,750 gm in weight were used. The blood urea concentration was within normal limits and the urine was free from albumin and casts.

14 Addis, T. *J Urol* **1** 263 (June) 1917

15 Addis, T. Renal Function and the Amount of Functioning Tissue, *Arch Int Med* **30** 378 (Sept) 1922

16 Addis, T., and Drury, D. R. *J Biol Chem* **55** 105 (Feb) 1923



Most of the various functional measurements were repeated three times before nephrectomy, three times at from fifteen to thirty-three days after the operation, and twice after from 106 to 126 days

Before each experiment no food was given for fifteen hours but water was left in the cages At about 9 a m 1 gm of urea per kilogram of body weight, dissolved in water in a 4 per cent concentration was given by stomach tube Three hours later an equal amount of water was administered The bladder was then catheterized and washed out At hourly intervals thereafter collections of urine were made by catheter and, after the volume had been measured, the bladder was washed out and the washings added to the urine At about the midpoint of the periods over which the urine was collected, blood was drawn from an ear vein into a vessel which contained a small amount of powdered oxalate Duplicate determination of the urea content of the urine and blood were made with the urease method

The following is one of the protocols in full

Rabbit 1 Weight, 2,700 gm Date, Aug 16, 1921  
 9 20 a m Given 67 c c 4 per cent urea solution by stomach tube  
 11 35 a m Given 67 c c of water by stomach tube  
 12 13 p m Catheterized and bladder washed  
 12 43 p m Bled about 5 c c  
 1 16 p m Catheterized and bladder washed  
 1 43 p m Bled about 5 c c  
 2 17 p m Catheterized and bladder washed  
 2 48 p m Bled about 5 c c  
 3 13 p m Catheterized and bladder washed

The urine collections were timed from the minute within which the last wash water was removed from the bladder, while for the blood collections the midpoint of the few minutes required to obtain enough blood was taken The volumes of urine and rates of urea excretion were then expressed as rates per hour, and the blood urea concentrations, when necessary, were corrected for the midpoint of each urine collec-

TABLE 1—Results of Experiment on Rabbit 1

Period, Hours	Volume, C c per Hour per Kg	Urine Urea, Mg per Hour per Kg	Blood Urea, Mg per 100 C c	Ratio $\frac{\text{Urine Urea}}{\text{Blood Urea}}$ per Kg
1	14.4	103.2	107.4	0.96
2	8.0	107.2	106.5	1.01
3	4.8	84.5	103.5	0.82

tion by plotting the three observations on coordinate paper Finally it was necessary to express the volume and urine urea figures as rates per kilogram of body weight per hour because during the three months over which the observations were continued there was some increase in body weight on account of growth The results in the before mentioned experiment are given in Table 1

The urea concentrating capacity was tested under conditions designed to put a strain on this function of the kidney. No water was given from 8 30 a m on one day until 3 30 p m of the following day, a period of thirty-one hours. At 8 30 a m, 5 30 p m, and at 8 30 a m of the next day 0.75 gm of urea per kilogram of body weight was given by stomach tube, dissolved in water in a 20 per cent concentration. The urine was collected by catheter at about 8 30 a m and also about 12 noon, and at 3 30 p m on the second day of the test. A sample of blood was obtained at the middle of the last period of urine collection. The following is one of the protocols.

Rabbit 2 Weight, 2,750 gm Date, July 27-28, 1921

8 30 a m, July 27, given 10.3 c c of a 20 per cent urea solution by stomach tube

5 30 p m, July 27, given 10.3 c c of a 20 per cent urea solution by stomach tube

8 50 a m, July 28, given 10.3 c c of a 20 per cent urea solution by stomach tube

9 03 a m, July 28, catheterized

12 06 p m, July 28, catheterized Urine collected

1 50 p m, July 28, bled

3 34 p m, July 28, catheterized Urine collected

TABLE 2—*Results of Experiment on Rabbit 2*

Time	Volume, C c	Urine Urea Concentration Gm per 100 C c
9 03 - 12 06	16	5.10
12 06 - 3 34	14	5.64

#### THE WEIGHT OF RENAL TISSUE AT THE COMMENCEMENT AND AT THE END OF THE EXPERIMENT

A comparison of different functional measurements can only be of use when there is some objective nonfunctional standard by which their relative value may be determined. This standard should be the amount of secreting tissue in the kidney because, from a clinical point of view at least, the value of any functional test will depend on whether or not we can use its results as a basis from which to estimate the amount of actively functioning renal tissue. In the normal kidney the amount of secreting tissue can be estimated with sufficient accuracy from the gross weight, but, as will be shown in detail in the last section of this paper, the usual relation between renal weight and amount of active tissue is disturbed under the special circumstances of our experiments, so that the gross weight somewhat underestimates the actual quantity of secreting tissue. Nevertheless we have used the weight of the kidney as our standard, since it was the only criterion available. We estimated the total renal weight before nephrectomy from the weight of the kidney we removed, and at the end of the

experiment the weight of the remaining kidney was obtained. In rabbits, estimations of the weight of both kidneys from the weight of one is not associated with any very great error. In twenty-two rabbits we found that the right kidney weighed on the average 6.58 gm. and the left 6.51 gm. The average error in deducing the weight of both from the weight of one was 2.1 per cent. and in only one case did the error exceed 4.3 per cent.

These kidney weights before and after nephrectomy are given in Table 3.

It will be noted that in from 106 to 126 days after nephrectomy the weight of renal tissue per kilogram body weight is 66 per cent of the original weight, instead of the 50 per cent which would have been found if there had been no compensatory hypertrophy. These initial and final weights give us two opportunities for a comparison of structure and function, but there is no standard for the functional measure-

TABLE 3—*Kidney Weights Before and After Nephrectomy*

Rabbit	Before Nephrectomy				After Nephrectomy (106-126 Days)		
	Kidney Weight per Kg. Body Weight, Gm.	Actual Weight of Kidney Removed, Gm.	Estimated Weight of Both Kidneys, Gm.	Body Weight, Gm.	Kidney Weight per Kg. Body Weight, Gm.	Actual Weight of Kidney Remaining, Gm.	Body Weight, Gm.
1	6.64	8.965	17.93	2,700	4.37	14.11	3,225
2	6.02	8.275	16.55	2,750	3.45	11.30	3,275
3	5.48	6.025	12.05	2,200	3.72	12.00	3,225
4	5.31	6.005	12.01	2,260	3.95	11.37	2,875
5	6.69	8.200	16.40	2,450	4.35	13.16	3,025
6	6.63	7.790	15.58	2,350	4.54	12.15	2,675
Average	6.13				4.06		
Percentage	100				66		

ments made between fifteen and thirty-three days after nephrectomy. It is certain, however, that the actual weight of renal tissue was between 50 per cent. and 66 per cent. of the weight before operation. The only quantitative measure of the rate of compensatory hypertrophy is that given by Hinman<sup>17</sup> for the rat. His figures show that the increase in the size of the kidney is not completed until between the twenty-eighth and the forty-second day. If the curve which can be constructed from his data is taken as the best available indication of the weight of the kidneys in our animals between fifteen and thirty-three days after nephrectomy, the average weight of the kidneys would be about 58 per cent. of the original value. These three weight values, expressed as 100 per cent. before nephrectomy, 58 per cent. from fifteen to thirty-three days after and 66 per cent. at the end of the experiment, have therefore been taken as the common standard by which to judge the relative value of each of our functional measurements.

<sup>17</sup> Hinman, F. Tr. Am. A. Gen.-Urin. Surg. **15**: 241, 1922.

## THE RATE OF UREA EXCRETION

It has been shown that the variability of the rate of urea excretion in the same and in different persons is greatly reduced after the administration of considerable amounts of urea,<sup>18</sup> so that it was to be expected that in our animals which had all been given 1 gm of urea per kilogram of body weight three hours before the observations were commenced, a greater uniformity in the rates of excretion should be found than in rates for similar time periods measured under ordinary conditions. The actual observations which are shown in Table 4 are indeed, if not remarkably constant, so much less variable than the

TABLE 4—*The Rate of Urea Excretion (Large Urine Volumes)*

Rabbit	Before			After (15-33 Days)			After (106-126 Days)		
	1st Hour, Mg per Kg	2d Hour, Mg per Kg	3d Hour, Mg per Kg	1st Hour, Mg per Kg	2d Hour, Mg per Kg	3d Hour, Mg per Kg	1st Hour, Mg per Kg	2d Hour, Mg per Kg	3d Hour, Mg per Kg
1	125 20 103 20 115 40	132 50 107 20 95 60	106 90 84 50 94 80	83 10 86 90 81 80	70 50 78 60	84 50 73 60 69 50	142 40 138 00	117 90 88 50	107 30
2		96 60 101 00 124 00	97 00 97 10 105 00	89 30 47 50 97 20	70 70 71 50 86 20	74 00 69 90 72 00	95 60 111 10	78 50 103 80	87 80 119 50
3	118 00 170 50 137 80	106 70 139 50 128 00	93 50 121 00 116 20	86 30 59 80 105 80	90 50 60 40 86 70	84 30 59 40 74 30	108 00 138 00	104 90 111 80	84 20 102 60
4	124 80 115 60 143 90	100 00 107 90 101 40	104 00 114 80 93 00	95 50 63 80 78 80	89 20 45 50 72 10	74 10 69 10 68 80	113 00 93 20	108 00 113 00	91 30
5		111 00 98 00 138 80	101 60 106 00 123 80	89 00 69 70 120 90	82 30 57 10 97 80	57 40 75 10 92 40	131 90 144 30	120 60 129 30	112 70
6	139 20 128 20 141 10	124 20 127 30 135 70	117 00 133 90 104 80	87 40 86 50 96 50	64 40 86 50 84 00	92 30 87 40 81 80	140 90	134 50 116 30	104 50 115 70
Average	127	115	105	85	76	76	124	111	103
Grand average		117 0			78 8			112 4	
Average per cent		100			69			98	
Renal weight, per cent		100			58			66	

rates usually recorded as to encourage the hope that a simple measurement of the rate of urea excretion, if carried out under these special conditions, might allow deductions as to the amount of renal tissue

It will be noted that the average rate decreases from 100 per cent to 68.6 per cent in from fifteen to thirty-three days after nephrectomy, a reduction which is not far from the 58 per cent of renal tissue estimated as present at that time. But the results of the last experiments carried out just before the animals were killed give the clearest indication that the rate alone, even under these conditions of strain, is not a reliable indication of the amount of renal tissue, since the average rate at that time was found to be 98 per cent of the rate

with both kidneys, although the renal tissue was reduced to 66 per cent

The rates of urea excretion which are given in Table 4 were obtained during the course of a diuresis, induced by the administration of urea and water. The volumes of urine were therefore high and the concentrations of urea in the urine were low. But we have also rates measured under the opposite conditions, that is, with low urine volumes and high concentrations of urea in the urine. These are given in Table 5.

Although these observations are few in number, they are quite enough to show that under these conditions there is no relation between the rate of urea excretion and the amount of renal tissue. The rates are, in fact, uniformly higher with 66 per cent of renal weight than with 100 per cent, and with 58 per cent they are not uniformly

TABLE 5—*The Rate of Urea Excretion (Small Urine Volumes)*

Rabbit	Before, Mg per Kg	After (8-26 Days) Mg per Kg	After (112-123 Days) Mg per Kg
1	78.6	82.4	96.2
2	85.0	78.0	86.4
3	95.4	69.5	90.6
4	78.6	61.6	98.4
5	81.8	85.5	100.0
6	80.8	79.6	132.6

TABLE 6—*Blood Urea Concentration Under Ordinary Conditions*

Rabbit	Before, Mg per 100 C c	After (15-33 Days) Mg per 100 C c
1	29	42
2	37	22
3	30	36
4	33	57
5	23	20
6	29	28

lower. It is noteworthy that, according to theories of urea excretion which have attained a wide currency, the rate should vary with the amount of renal tissue under the conditions we imposed, which were such as to induce unusually high concentrations of urea in the urine. In fact, Ambard and Papin<sup>9</sup> on the basis of such theoretic considerations predicted that after the removal of one kidney the rate of urea excretion should be proportionately reduced under these conditions.

#### THE BLOOD UREA CONCENTRATION

If the blood urea concentration can be taken as a measure of the amount of urea secreting tissue in the kidney it should increase after unilateral nephrectomy. A complete agreement with the renal weight standard would give a 42 per cent and a 34 per cent increase.

When the blood was taken under ordinary conditions there was no definite increase at all (Table 6).

When the blood was taken after the administration of urea and water (Table 7) there was a doubtful increase (5 per cent) from fifteen to thirty-three days after nephrectomy, but from 106 to 126 days after the operation, although there was then more renal tissue, a 24 per cent increase was found. This latter increase cannot therefore be directly owing to the changes in renal structure. It does, however, explain the practically normal rate of urea excretion noted at that time.

When the blood was taken after twenty-nine and one-half hours of abstention from fluids and five hours after the last of three doses

TABLE 7—*Blood Urea Concentration After the Administration of Urea and Water*

Rabbit	Before			After (15-33 Days)			After (106-126 Days)		
	1st Hour	2d Hour	3d Hour	1st Hour	2d Hour	3d Hour	1st Hour	2d Hour	3d Hour
1	109.3	95.9	72.3	104.6	99.1	87.7	135.0	123.0	
	107.4	106.5	103.5	114.0		99.9	124.8	132.3	119.7
	94.2	94.2	82.8	141.0	120.0	115.5			
2	118.8	111.6	108.6	122.0	115.5	120.0	132.0	129.0	120.0
	105.6	103.0	103.0	126.0	117.0	114.0	131.9	138.9	135.3
	137.2	122.8	111.2	121.5	107.7	97.0			
3	96.4	90.5	81.5	89.1	81.0	76.0	113.1	110.1	98.1
	107.6	98.1	91.1	102.0	95.0	94.0	129.0	132.0	114.0
	111.0	107.4	102.9	127.2	124.6	116.7			
4	118.6	103.8	115.6	109.2	106.8	106.8	157.5	141.0	
	130.2	130.2	128.2	130.5	121.5	112.0	168.0	144.0	141.0
	101.4	101.4	96.6	118.2	113.1	108.7			
5	108.7	98.4	92.5	118.4	87.0	84.0	119.4	102.0	
	83.3	76.2	73.4	116.0	99.0	96.0	132.0	117.0	105.0
	111.0	105.0	94.8	110.7	110.2	103.5			
6	99.9	91.6	83.4	120.0	105.0	81.0	114.0	102.0	94.5
	108.5	105.0	95.6	132.9	121.2	109.5		117.0	102.0
	100.3	90.5	84.8	122.0	114.5	106.0			
Average	108	102	96	118	108	101	133	124	113
Grand average		103.8			109.2			128.4	
Average per cent		100			105.2			123.5	
Renal weight, %		100			58			66	

of 0.75 gm of urea per kilogram of body weight, there was a 33 per cent increase of blood urea concentration from fifteen to thirty-three days after nephrectomy, and a 44 per cent increase from 106 to 123 days after (Table 8).

In general, therefore, it would seem that the loss of 50 per cent of the renal tissue does not under ordinary conditions lead to any noteworthy increase in blood urea concentration. It should be noted that, in the first few days after such an operation as nephrectomy, some increase in blood urea concentration might be expected because of the increased protein catabolism, which has been shown to occur under these conditions.<sup>19</sup> A study of the variations of blood urea concentration

in normal persons, previously published,<sup>20</sup> and in particular, some recent work in this laboratory has convinced us that the level of blood urea concentration tends to vary with the rate of protein catabolism. The increase in blood urea concentration, which Hohlweg<sup>10</sup> found after unilateral nephrectomy, and the increase Addis and Watanabe<sup>13</sup> observed shortly after ligation of one ureter might well be explained on these grounds and should not, we think, be regarded as a direct result of the removal of renal tissue. But under conditions of strain there is some indication that the decrease in renal tissue may lead to a slight increase in blood urea concentration. The evidence is not conclusive, however, for there was only a 5 per cent increase after urea and water, and the meaning of the 33 per cent increase, found after abstention from fluids, is not quite clear. Such conditions are associated with an increase in protein catabolism which may have been more pronounced

TABLE 8—*Blood Urea Concentration After Abstention From Fluid and After Urea Administration*

Rabbit	Before, Mg per 100 C c	After (8-26 Days) Mg per 100 C c	After (110-123 Days) Mg per 100 C c
1	69	93	104
2	74	106	137
3	62	69	87
4	86	101	102
5	50	81	74
6	69	80	85
Average	68	88	98
Average per cent	100	133	144
Renal weight, per cent	100	58	66

after the operation than before. It is at least quite evident from the figures that under no conditions is there any fixed quantitative relation between the degree of increase in blood urea concentration and the degree of reduction in renal tissue.

#### THE URINE UREA CONCENTRATION

The inability of the kidney to produce urine which has a high concentration of solids is one of the functional indications of disease which has been used more widely, and for a longer time than perhaps any other. In the form of an inability to produce high concentrations of urea in the urine it has been particularly prominent during and since the war. But as a renal test it suffers from the disadvantage of complexity. For the concentration of urea in the urine depends on the rate of water as well as on the rate of urea excretion, and the very

20 Addis, T, and Watanabe, C K. The Causes of the Variation in the Concentration of Urea in the Blood of Young Healthy Adults, Arch Int Med 19 507 (April) 1917

many purely extrarenal factors which may influence water excretion will commonly prevent us from drawing unqualified deductions as to the condition of the kidney from any measurement involving volume rates. It has also been shown by Ambard and Papin<sup>9</sup> that the removal of one kidney is not followed by any decrease in the urea concentration in the urine, a result which might indeed have been anticipated, since there is no evidence in the same or in different species of animals of any such association between the amount of renal tissue and the level of the concentration of urea in the urine as exists between the weight of the kidney and the rate of urea or of water excretion.

On the other hand, Bradford<sup>21</sup> found that the urine urea concentration was less than normal when one kidney and a considerable part of the remaining kidney was excised. His tables show that this effect was not produced by any decrease in the rate of urea excretion. On the contrary, the amounts of urea excreted were appreciably larger

TABLE 9—*Maximal Urine Urea Concentrations After Abstention From Fluid and After Urea Administration*

Rabbit	Before, Gm per Cent	After (8-26 Days) Gm per Cent	After (110-123 Days) Gm per Cent
1	5.64	5.28	6.87
2	6.15	5.61	4.26
3	6.66	3.93	7.14
4	4.87	4.74	5.97
5	5.03	6.60	8.36
6	3.73	5.96	8.36
Average	5.35	5.35	6.84
Average per cent	100	100	128
Renal weight per cent	100	58	66

than before the operation, but the concentration was lower because of a relatively greater increase in water excretion.

Although the degree of reduction in renal tissue was much less pronounced in our experiments than in Bradford's, we thought that we might possibly be able to observe some effect on the urine urea concentration if we imposed conditions which would strain the urea concentrating capacity of the remaining kidney. Therefore we not only gave no fluids for a considerable period of time, but we administered three successive doses of 20 per cent urea, thus depleting the body of water, and at the same time increasing the amount of urea which had to be excreted. The highest urine urea concentrations found in each experiment are shown in Table 9.

These results show that, even under these special conditions, a reduction of renal tissue to about 58 per cent of its original value has no appreciable effect on the concentration of urea in the urine.

21 Bradford J Physiol 23 415, 1898-1899



Toward the end of the period of abstention from fluids, and at the middle of the last period over which urine was collected, a sample of blood was drawn in order that the effect of the removal of renal tissue on the quotient obtained by dividing the urine urea concentration by the blood urea concentration might be observed. The results are given in Table 10.

The values of the quotient are too variable and the number of observations is too small to allow us to attach very much importance to the average results, though it is very likely that the operation was responsible for the reduction in the quotient value. From the fact

TABLE 10—The Concentration Quotient  $\frac{\text{Urine Urea Concentration}}{\text{Blood Urea Concentration}}$

Rabbit	Before			After (8-26 Days)			After (112-123 Days)		
	Urine %, Mg per 100 C c	Blood %, Mg per 100 C c	Quotient $\frac{\text{Urine \%}}{\text{Blood \%}}$	Urine %, Mg per 100 C c	Blood %, Mg per 100 C c	Quotient $\frac{\text{Urine \%}}{\text{Blood \%}}$	Urine %, Mg per 100 C c	Blood %, Mg per 100 C c	Quotient $\frac{\text{Urine \%}}{\text{Blood \%}}$
1	5,640	69	82	5,280	93	57	6,870	104	66
2	6,150	74	83	5,610	106	53	4,200	137	31
3	6,660	62	108	3,930	69	57	7,140	87	82
4	4,870	88	57	4,740	101	47	5,970	102	59
5	5,030	50	106	6,600	81	82	8,360	74	113
6	3,720	69	54	5,960	80	75	8,800	83	98
Average			82			62			75
Average per cent			100			76			92
Renal weight per cent			100			58			66

that in the final experiment the average quotient was as high as 92 per cent, when the renal weight was only 66 per cent, it is clear that there is no dependable relation between this functional measurement and the amount of renal tissue.

#### THE VOLUME OF URINE

The volume of urine was measured after the administration, by stomach tube, of 50 c c of water per kilogram of body weight, 25 c c three hours, and 25 c c just before the collections of urine were commenced. This is, of course, a large amount of water, equivalent to 3,500 c c for a man of average weight. The results are given in Table 11.

Under these conditions of strain there is, on the average, a reduction in the rate of water excretion, which, though not of the same degree as the reduction in renal tissue, yet appears to run parallel to it. But when the individual experiments are compared, the significance of these averages is lessened, for sometimes no appreciable change in volume occurs after nephrectomy and sometimes the volume may even be increased.

The volume of urine was also measured under conditions altogether different from those we have just described, in that they were designed

to lead to a great reduction in the rate of water excretion. No fluids were given for a period of thirty-one hours, with the exception that 3.75 cc per kilogram of a 20 per cent solution of urea was given by stomach tube at 8.30 a. m. and at 5.30 p. m. of the first day, and at 8.30 a. m. of the second day. Two three-hour collections of urine were obtained by catheter during the last six hours of the experiment. The smallest volumes obtained in each rabbit are given in Table 12.

TABLE 11—*The Volume of Urine After the Administration of Water and of Urea*

Rabbit	Before			After (15-33 Days)			After (100-120 Days)		
	1st Hour, Cc per Kg	2d Hour, Cc per Kg	3d Hour, Cc per Kg	1st Hour, Cc per Kg	2d Hour, Cc per Kg	3d Hour, Cc per Kg	1st Hour, Cc per Kg	2d Hour, Cc per Kg	3d Hour, Cc per Kg
1	11.50 14.40 20.40	11.50 8.00 11.50	4.10 4.80 5.20	14.20 12.00 12.00	12.30 7.90	7.50 5.70 3.80	21.40 15.10	8.10 9.80	7.20
2	5.90 11.10	10.20 10.30 8.00	9.20 8.00 7.60	14.20 6.80 14.90	12.00 8.90 9.90	9.10 6.60 4.10	7.80 8.00	5.20 7.80	3.80 6.10
3	29.80 20.50 18.00	12.30 6.80 11.80	8.20 3.60 6.30	14.20 12.50 16.90	5.40 3.40 9.10	3.40 4.80 3.80	12.80 19.40	9.10 6.90	4.10 5.00
4	19.00 16.80 22.20	9.80 14.30 9.10	7.60 5.70 3.60	18.40 11.70 12.10	9.70 4.60 5.30	5.20 4.90 3.70	10.60 13.80	11.20 16.20	5.60
5	6.20 19.70	11.70 11.60 11.00	8.40 12.90 4.20	19.60 8.90 21.00	6.80 8.30 7.60	2.60 6.30 3.50	18.20 23.20	8.70 5.30	3.70
6	16.90 10.30 18.70	4.50 13.50 8.00	4.00 5.50 2.60	18.30 12.60	5.30 7.40	4.60 3.00 3.00	19.70	7.70 6.00	3.40 4.60
Average	16.30	10.20	6.20	14.10	7.60	4.80	15.40	8.50	4.20
Grand average		10.90			8.90			9.50	
Average per cent		100			81.6			87.2	
Renal weight, %		100			58			66	

TABLE 12—*The Volume of Urine After Abstention From Fluids*

Rabbit	Before, Cc per Kg per Hour	After, Cc per Kg per Hour	After, Cc per Kg per Hour
1	1.47	0.44	1.40
2	0.89	1.20	1.76
3	1.11	0.54	1.27
4	1.38	0.39	1.48
5	1.40	1.04	1.19
6	1.13	1.18	1.59

From the experiments of Bradford and others, and from the general body of clinical experience with patients whose kidneys have been almost entirely destroyed, a reduction in renal tissue should lead to an increase in the volume of urine under such conditions as we set. There is no indication of any such increase in the rate of water excretion in the figures given in Table 12. It must be concluded that the volume of urine after abstention from fluids, even under these particularly favorable conditions, gives no indication of any reduction in the amount of renal

tissue This type of functional derangement is evidently the result of a much more pronounced decrease in secreting tissue than we produced in our experiments

The "volume quotients," that is, the number of times by which the volume after much fluid has been given, exceeds the volume when no fluids are taken, showed no consistent change after nephrectomy This is in conformity with the results of similar observations on patients with "Bright's disease," for it has been shown that considerably more than half the renal tissue must be destroyed, before there is any appreciable decrease in the value of this quotient <sup>22</sup>

THE RATIO  $\frac{\text{Urea in one hour's urine}}{\text{Urea in 100 c c of blood}}$

This measurement has been shown to vary in direct relation to the amount of secreting tissue in the kidney,<sup>1</sup> and it was therefore to be expected that there should be a close approximation between the

TABLE 13—The Ratio  $\frac{\text{Urea in one hour's urine}}{\text{Urea in 100 c c of blood}}$  After the Administration of Urea and of Water

Rabbit	Before			After (15-33 Days)			After (106-126 Days)		
	1st Hour per Kg	2d Hour per Kg	3d Hour per Kg	1st Hour per Kg	2d Hour per Kg	3d Hour per Kg	1st Hour per Kg	2d Hour per Kg	3d Hour per Kg
1	1.15	1.38	1.48	0.80	0.71	0.96	1.05	0.96	
	0.96	1.01	0.82	0.75		0.74	1.11	0.67	0.90
	1.23	1.01	1.14	0.57	0.66	0.60			
2		0.87	0.90	0.73	0.61	0.62	0.72	0.61	0.73
	0.96	1.05	0.94	0.40	0.61	0.61	0.78	0.75	0.88
	0.90	0.89	0.94	0.80	0.80	0.74			
3	1.23	1.18	1.15	0.97	1.12	1.09	0.95	0.95	0.86
	1.59	1.42	1.33	0.59	0.63	0.63	1.07	0.85	0.90
	1.24	1.19	1.13	0.83	0.70	0.64			
4	1.05	0.96	0.90	0.80	0.75	0.70	0.72	0.77	
	0.89	0.83	0.89	0.49	0.37	0.62	0.58	0.79	0.65
	1.42	1.00	0.96	0.67	0.64	0.63			
5		1.14	1.10	0.75	0.95	0.68	1.12	1.18	
	1.18	1.39	1.45	0.60	0.58	0.80	1.09	1.11	1.07
	1.25	1.18	1.15	1.09	0.88	0.89			
6	1.39	1.36	1.40	0.73	0.61	1.14	1.10	1.32	1.10
	1.18	1.21	1.40		0.71	0.80	1.13	0.95	1.13
	1.41	1.50	1.24	0.79	0.73	0.77			
Average	1.19	1.14	1.13	0.73	0.71	0.76	0.92	0.91	0.91
Grand average		1.15			0.74			0.91	
Average per cent		100			63.4			79.4	
Renal weight, per cent		100			58			66	

decrease in the value of the average ratio and the diminution in the amount of renal tissue following nephrectomy The results given in Table 13 do indeed indicate a fair approximation between the measure of function and structure

<sup>22</sup> Addis, T The Clinical Significance of Abnormalities in Urine Volumes, Arch Int Med 31 783 (June) 1923

Table 14, which summarizes all of the results, shows that the urea ratio is the only functional method which gives even an approximate measure of the amount of renal tissue

The agreement between the average ratio value and the average weight of the kidney is not so close as might be anticipated. At the first measurement after nephrectomy the ratio indicates 5 per cent, and

TABLE 14—*Summary of Functional and Structural Measurements*

	Before, per Cent	After (15-33 Days) per Cent	After (100-126 Days) per Cent
Weight of renal tissue	100	58	63
Ratio $\frac{\text{Urea in 1 hour's urine}}{\text{Urea in 100 cc of blood}}$	100	63	70
Rate of water excretion	100	82	87
Concentration quotient $\frac{\text{Urine \%}}{\text{Blood \%}}$	100	76	62
Maximal urine urea concentration	100	100	128
Blood urea concentration	100	105	124
Rate of urea excretion	100	69	68

at the second 13 per cent more renal tissue than is shown by the weight of the kidney. Such discrepancies may in part or altogether be explained by the peculiar quantitative relationships between various parts of the structure of the remaining kidney. These structural changes are dealt with in the next section, since they have a significance which transcends their relation to our experiments.

### CONCLUSIONS

1 The amount of renal tissue was decreased by a unilateral nephrectomy. Various methods for measuring renal function were used before and after the operation. The measurements were carried out under conditions which involved strain and which excluded, so far as possible, the influence of factors which stimulate or depress renal activity. The results were compared with the weight of renal tissue.

2 It was found that the only functional method which gave an approximate measure of the structural change was the determination

$$\frac{\text{urea in one hour's urine}}{\text{urea in 100 cc of blood}}$$

# THE REGULATION OF RENAL ACTIVITY

## X THE MORPHOLOGIC STUDY

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The morphologic changes which follow the extirpation of one kidney, and which result in a compensatory hypertrophy of the remaining organ, have been even more extensively studied than the functional disturbances which obtain under such conditions. The following study adds, therefore, but little to our knowledge of the changes involved, but is of interest chiefly in that it correlates these changes with the functional disturbances described in the first section of this paper, and also in that it makes clear the reason for certain discrepancies which are found when the weight of the kidney is taken as a measure of the amount of functioning tissue present in it.

As examples of earlier morphologic work two studies may be briefly cited which summarize our knowledge of the subject. Lorenz<sup>1</sup> found that the increase in the size of the remaining kidney was chiefly due to an increase in the volume of the cortex. This was the result of an hypertrophy and, in young growing animals, of a slight hyperplasia of the glomeruli and convoluted tubules. The lesser increase in the volume of the medulla was due to a dilation of the lumen of the tubules contained in it, there being no increase in the number or size of the constituent cells.

Galeotti and Villa-Santa<sup>2</sup> came to essentially the same conclusions from their studies, though they place more emphasis on the increase in the number of glomeruli in young animals than did Lorenz. They did not, however, observe these hyperplastic processes in adult animals.

A study of the kidneys from the experiments described in the first part of this paper reveals similar results. The glomeruli and convoluted tubules were definitely enlarged, with no evidence of increase in their number, while the ascending limbs of Henle's loop and the collecting tubules showed only a slight increase in size.

## METHODS

The kidneys, after removal at operation and after the death of the animal, were cut in transverse slices and fixed in 10 per cent neutral

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1 Lorenz, H. *Ztschr f klin Med* **10** 545, 1885

2 Galeotti, G., and Villa-Santa, G. *Beitr z path Anat u z allg Path* **31** 121, 1902

formaldehyd Frozen sections were prepared and stained with hematoxylin and Van Gieson's mixture and then mounted in Farrant's fluid In this way alcohol was avoided, so that little if any shrinkage or distortion of the tissues occurred

The different structures were then measured with an eye-piece micrometer In order to obtain the correct measurements such as diameters or the height of epithelium, measurements were only taken on tubules, which were cut in perfect cross section or in a plane which passed through their longitudinal axes As such a diameter will be the greatest one, it was comparatively easy to avoid confusion of these proper measurements with those which pass tangentially through a tubule or glomerulus and so do not represent the actual dimensions of the structure

The following measurements were made For tubules, the outside diameter from the membrana propria to the membrana propria, the

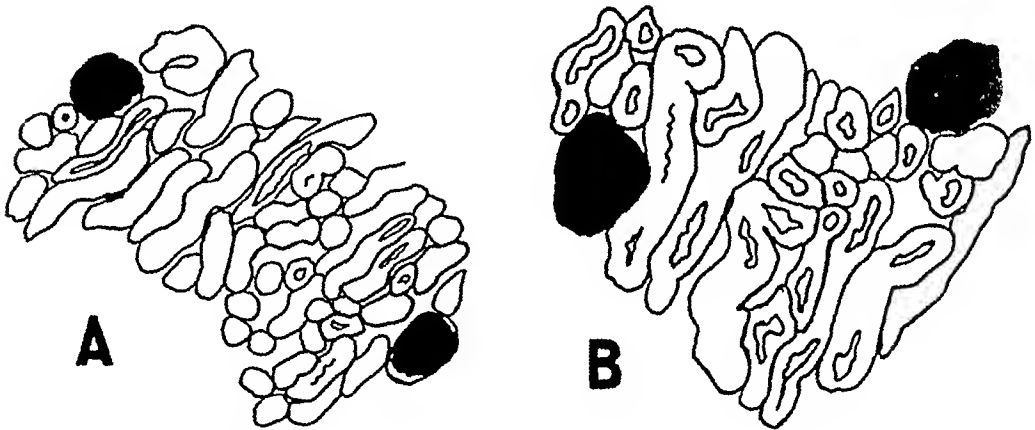


Fig 1—Microphotographs of the kidney removed at operation (a) and the other kidney at the end of the experiment (b) The larger tubules shown are convoluted tubules

least diameter of the lumen and the height of the epithelium from the membrana propria to the free surface In the case of the collecting tubule these measurements were made at the junction of the outer and inner zone For the glomeruli, the greatest and least diameters, including Bowman's space, were taken Besides these actual measurements the area of a typical cross section of the various tubules and of the glomerulus was calculated There is a certain inaccuracy in the determination of this value in the case of the tubules, as the formula used for the computation assumes that the lumen is a circle This is not always the case, as it may be flattened to form an oval or even stellate figure in cross-section As this error is a constant one and as our values are used only for comparing different tubules with each other, the effect of it may be neglected

TABLE 1—Measurements of Kidney Structures, Rabbit 4

	Convolved Tubule			Ascending Limb			Collecting Tubule			Glomerulus	
	D	d	E	D	d	E	D	d	E	Greatest Diameter	Least Diameter
Kidney Removed at Operation	1 00	0 0	0 50	0 80	0 10	0 35	1 10	0 30	0 40	3 00	2 60
	1 10	0 0	0 55	0 70	0 0	0 35	0 70	0 20	0 25	3 00	3 00
	0 80	0 0	0 40	0 70	0 20	0 25	0 70	0 0	0 35	3 20	2 50
	0 70	0 0	0 35	0 60	0 0	0 30	1 00	0 20	0 40	3 00	2 80
	0 80	0 0	0 40	0 80	0 20	0 30	0 80	0 30	0 25	3 00	2 50
	1 00	0 10	0 45	0 60	0 10	0 35	0 80	0 10	0 35	3 20	2 00
	0 80	0 10	0 35	0 60	0 20	0 20	1 10	0 30	0 40	3 50	2 50
	0 90	0 10	0 40	1 00	0 40	0 30	1 00	0 10	0 45	3 00	2 50
	0 80	0 20	0 30	0 80	0 20	0 30	0 90	0 10	0 40	2 80	2 50
	0 80	0 0	0 40	0 80	0 20	0 30	1 00	0 10	0 40	3 00	2 40
	0 90	0 30	0 30	0 90	0 30	0 30	0 80	0 0	0 40	3 50	2 60
	0 70	0 0	0 35	0 80	0 0	0 40	1 00	0 20	0 40	3 50	2 80
	0 70	0 10	0 30	0 70	0 10	0 30	1 10	0 40	0 35	3 20	2 60
	0 65	0 0	0 30	0 70	0 30	0 20	1 00	0 10	0 45	3 00	3 00
	0 80	0 10	0 40	0 70	0 10	0 30	1 00	0 10	0 45	3 20	3 00
	0 70	0 10	0 35	0 90	0 20	0 40	0 90	0 20	0 30	3 00	2 00
	0 80	0 0	0 35	0 90	0 15	0 20	0 90	0 50	0 40	3 00	2 00
	0 70	0 10	0 37	0 80	0 25	0 30	0 80	0 10	0 30	3 20	3 00
	0 65	0 0	0 38	0 80	0 10	0 30	1 00	0 20	0 30	3 00	3 00
	0 80	0 10	0 36	0 85	0 10	0 30	0 90	0 10	0 40	4 00	2 00
Average	0 80	0 065	0 37	0 77	0 16	0 30	0 92	0 17	0 37	3 16	2 56
Kidney at End of Experiment	1 30	0 0	0 70	1 40	0 50	0 30	0 80	0 20	0 30	4 00	2 50
	1 10	0 30	0 45	1 00	0 60	0 20	1 00	0 30	0 35	3 80	2 60
	1 20	0 50	0 40	1 00	0 40	0 30	1 10	0 50	0 30	3 60	3 20
	1 30	0 20	0 60	0 70	0 10	0 30	1 10	0 50	0 20	4 00	3 00
	1 10	0 20	0 45	0 80	0 30	0 25	1 40	0 80	0 30	3 20	3 40
	1 20	0 10	0 60	1 00	0 40	0 30	1 10	0 50	0 30	3 80	3 00
	1 30	0 60	0 40	1 20	0 60	0 20	1 20	0 10	0 30	3 60	3 00
	1 10	0 50	0 34	0 80	0 50	0 25	0 80	0 70	0 35	4 00	3 00
	1 20	0 60	0 40	0 60	0 60	0 30	0 90	0 30	0 25	3 50	3 40
	1 30	0 40	0 50	1 20	0 80	0 20	1 00	0 40	0 30	3 60	3 60
	1 10	0 60	0 30	0 90	0 45	0 25	1 20	0 40	0 30	4 00	3 50
	1 00	0 30	0 35	1 10	0 50	0 25	1 00	0 20	0 40	3 70	3 20
	1 10	0 30	0 35	1 10	0 60	0 30	0 80	0 30	0 40	3 80	3 00
	1 10	0 30	0 40	0 90	0 30	0 30	0 90	0 30	0 25	4 00	3 20
	1 20	0 40	0 40	1 00	0 50	0 20	1 10	0 50	0 30	4 00	4 00
	1 10	0 40	0 50	0 90	0 40	0 30	0 90	0 40	0 40	3 00	2 00
	1 10	0 30	0 50	0 95	0 60	0 20	0 80	0 30	0 20	3 00	3 00
	1 20	0 30	0 40	1 10	0 30	0 20	1 20	0 40	0 30	4 00	3 00
	1 30	0 40	0 40	0 80	0 50	0 30	1 10	0 40	0 30	4 00	2 00
	1 00	0 30	0 45	0 95	0 40	0 30	0 95	0 40	0 35	3 00	3 00
Average	1 16	0 35	0 44	0 95	0 46	0 26	1 01	0 39	0 31	3 68	3 08

TABLE 2—Dimensions of Various Elements in Remaining Kidney Expressed as Percentage Increases of Value Observed in Kidney Removed at Operation

	Rabbit						Average
	1	2	3	4	5	6	
Increase in weight of kidney per kilo gram of body weight	+66	+ 57	+ 67	+ 74	+ 65	+ 68	+ 66
External diameter of tubule							
Convolved tubule	+16	+ 37	+ 21	+ 45	+ 34	+ 45	+ 33
Ascending limb	+25	+ 28	+ 27	+ 23	+ 27	+ 25	+ 26
Collecting tubule	+ 9	+ 18	0	+ 9	+ 18	- 10	+ 7
Diameter of lumen							
Convolved tubule	+40	+100	+ 60	+440	+ 86	+122	+141
Ascending limb	+67	+100	+140	+185	+300	+ 46	+139
Collecting tubule	+ 2	+ 33	+ 42	+129	+ 33	- 16	+ 37
Height of epithelium							
Convolved tubule	+19	+ 33	+ 6	+ 19	+ 23	+ 13	+ 18
Ascending limb	-12	- 6	- 11	- 13	- 55	- 20	- 19
Collecting tubule	+18	- 17	- 10	- 16	- 17	- 10	- 7

## RESULT OF EXAMINATION

Twenty tubules of each type and twenty glomeruli were measured in each kidney of each animal. The consistency of the measurements allowed the assumption that such a number is sufficient to represent accurately the true values of the structures. Table 1 gives the complete measurements in a typical animal.

The unit of measurement is an arbitrary one, the amount of space covered by one division of the micrometer used. This was not reduced to microns, as there seemed to be no need for absolute values, our interest being entirely in a comparison of the various structures. Figure 1 illustrates the increase in size of the convoluted tubules and of the glomeruli in the kidney at the end of the experiment (*B*) as compared to these structures in the normal kidney removed at the operation (*A*). The figures were prepared by photographing sections of the two organs with the same magnification. The outlines of the

TABLE 3—*Cross Section Area of Tubules and Glomerulus of the Hypertrophied Kidney Expressed as Percentages of the Total Original Value of These Structures as They Existed in Both Kidneys Before the Operation (a value in the Table of 50 Per Cent Indicates That There Was No Increase in the Cross Section Area of the Structure)*

	Rabbit						Average
	1	2	3	4	5	6	
Weight of kidney	60	57	67	74	65	68	66
Convoluted tubule	59	93	68	97	83	91	82
Ascending limb	59	71	53	54	60	61	59
Collecting tubules	61	51	50	55	67	39	53
Glomerulus	63	63	57	71	50	57	60

structures were then traced on the photographic print with india ink and the details removed by bleaching with compound solution of iodine and "hypo."

Table 2 is a summary of the findings in the six animals. The results are expressed as percentage increases or decreases in the dimensions of the structures of the hypertrophied kidney as compared to those in the kidney removed at operation. In Table 3 is given the cross section area of the different structures for all the animals as calculated from the actual measurements. The results are expressed here in a different way than in Table 2. The cross section area of the structure, as found in the hypertrophied kidney at the end of the experiment, is given as the percentage of the total original cross section area of the structure concerned as it existed in the two kidneys of the animal before the nephrectomy. The advantage of this method of expression will be shown in the discussion of our results.

The charts represent graphically a summary of the average findings in the whole group of animals.



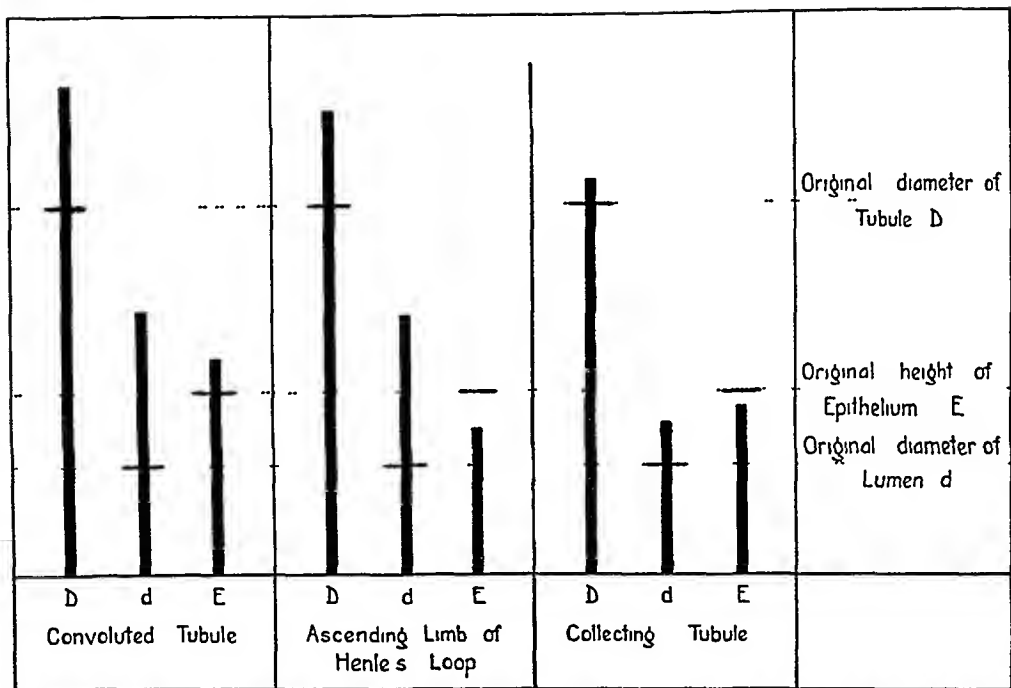


Fig 2—Increases in the dimensions of the hypertrophied kidney as compared with the kidney removed at operation. The horizontal dotted lines represent the original values in the removed kidney: the uppermost, the original diameter of the tubule  $D$ , the middle one, the height of the epithelium of the tubule  $E$ , the lowest, the diameter of the lumen of the tubule  $d$ . The heavy vertical lines show the increase or decrease over these values that were found in the hypertrophied kidney at the end of the experiment.

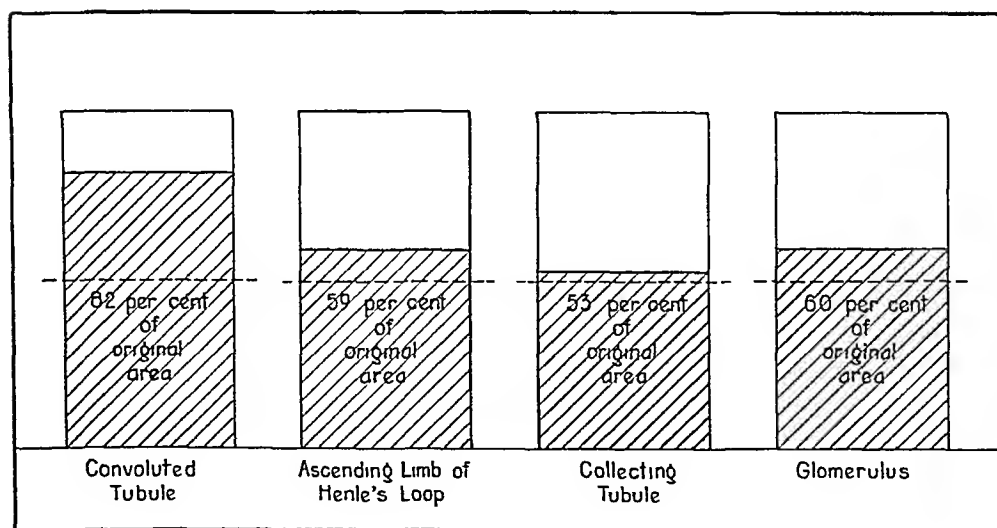


Fig 3—Relative replacement of the original cross-section area values of the different structures by the process of hypertrophy. The large rectangle represents the total original cross-section area in the two kidneys before nephrectomy. The shaded portion shows to what extent, expressed as a percentage, this value had been recovered by the growth of the structure. The dotted line shows the value (50 per cent) that existed immediately after the removal of one half of the kidney substance in the form of one kidney. The shaded portion lying above the dotted line therefore represents the degree of hypertrophy of the structure concerned.

Figure 2 shows the diameter of the tubules and the height of their lining epithelium and is based on Table 1. The upper horizontal line represents the original diameter of the tubule D, the middle one, the original height of its epithelium E. The lower dotted line represents the original diameter of the lumen. The vertical lines show in the case of each tubule the comparative value of the three dimensions in the hypertrophied kidney.

It will be observed that in the case of the convoluted tubule there is a definite increase in the outside diameter of the tubule. The diameter of the lumen is also more than twice its original size, yet in spite of this dilatation the lining epithelium is considerably thicker than the original epithelium.

Entirely different relations are found in the other two portions of the tubule. In the ascending limb of Henle's loop there is a definite increase in the diameter of the tubule and a marked increase in the diameter of the lumen. The epithelium, however, is thinner than normal, in other words, the increase in the size of the tubule as a whole is in great part due to a simple dilatation with a resulting stretching and thinning of its wall. The same dilatation and thinning of the epithelium is found in the collecting tubules but to a lesser degree.

In Figure 3 average cross-section areas of the various tubules and of the glomeruli are shown. The larger rectangle represents the area of the cross-section of the structure before operation and includes both kidneys. The smaller contained rectangle shows to what degree this original cross-section area had been replaced by the process of hypertrophy. This comparison assumes that there has been no increase in the number of renal units. We found no evidence of such an increase of either tubules or glomeruli, and this agrees with the findings of other investigators who have used adult animals.

It will be observed that the only part of the renal tubule showing a definite hypertrophy is the convoluted portion. In the average animal this process had so increased the cross-section area that at the end of the experiment the single kidney contained within 18 per cent of the cross-section area of the two kidneys before the operation. The condition of the ascending limb of Henle's loop and the collecting tubule is represented by an increase to 59 and 53 per cent, respectively. This represents only a slight change from the 50 per cent value, which obtained immediately after the removal of half the kidney tissue at the operation.

The glomerulus shows some increase in size, more than either the ascending limb or the collecting tubule, but considerably less than did the convoluted tubule. At the end of the experiment the cross-section area of glomerulus was 60 per cent of the combined value which existed before the removal of one kidney.

Our findings therefore confirm the earlier conclusions of Lorenz and of Galeotti and Villa-Santa. There is a true hypertrophy of the convoluted tubules and of the glomerulus. The enlargement of the ascending limbs of Henle's loop and of the collecting tubules is largely due to a dilatation.

#### COMMENT

The results of this morphologic study are of interest in relation to certain general problems of kidney function. Microchemical studies have led to the conception that in the case of urea at least two processes occur in its excretion, first a passage of it through the glomerular membrane and, of even greater importance, an excretion of it into the urine by the cells of the convoluted tubules. This theory is supported by the demonstration with xanthidol of urea within Bowman's space and in the protoplasm of the cells of the convoluted tubules (Oliver<sup>3</sup>). These experiments have since been repeatedly confirmed (Stubel,<sup>4</sup> Piras,<sup>5</sup> Walter<sup>6</sup>).

It has been shown further that the excretion of urea requires work on the part of the kidney. These two facts will account for the hypertrophy which develops in the glomerulus and the convoluted portion of the renal tubule. The other portions of the renal unit would appear to play a passive rôle in the excretion of urea, or at least the processes that may occur there must be simpler physical ones that require little work on the part of their cells, as the excessive strain thrown on the single kidney produced no response in them such as is almost constantly observed when functioning tissues are hyperactive over long periods. The results of the present study therefore lend further support to the dualistic conception of renal excretion by the glomerulus and by the convoluted tubules.

Furthermore, the morphologic findings explain the discrepancy noted in the first part of this paper between the functional measurement of the amount of renal tissue after nephrectomy and the weight of the remaining kidney. Taylor, Drury, and Addis<sup>7</sup> have shown that in normal rabbits the measurement of function as expressed by the ratio  $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c.c. of blood}}$  is directly proportional to the amount of secreting tissue in the kidneys as expressed by their weight. As will be seen in Table 2 of the first section of this paper, though the ratios and weights in the present experiments do vary with each other and are in

3 Oliver, J. *J. Exper. Med.* **33** 177 (Feb.) 1921.

4 Stubel, H. *Anat. Anz.* **54** 236, 1921.

5 Piras, A. *Arch. d. fisiol.* **20** 237, 1922.

6 Walter, K. *Arch. f. d. ges. Physiol.* **198** 267, 1923.

7 Taylor, F. B., Drury, D. R., and Addis, T. *Am. J. Physiol.* **65** 55 (June)

much closer agreement than is found when the function is expressed by any other means, nevertheless the average final ratio is larger (79 per cent of the original value before operation) than is the final average weight (66 per cent).

In the light of our knowledge of the anatomic relations which exist in the hypertrophied kidney this discrepancy is obviously due to the fact that the weight of the hypertrophied kidney is not a true measure of the relative amount of functioning tissue in it. Accepting the theory previously advanced that excretion of urea occurs only in the glomerulus and convoluted tubule, it is evident that in the hypertrophied kidney, where there has occurred a selective increase in the amount of these two structures without a corresponding increase in the other portions of the kidney, a given weight of kidney substance will contain a greater amount of secreting tissue than does a normal kidney. Hence, if the amount of tissue is measured by its function a higher result per unit of weight is obtained than in the normal organ.

The cross-section area of the structure most actively concerned in excretion, the convoluted tubule, probably represents more accurately the relative secretory capacity of the hypertrophied kidney than does the weight which includes much that plays no part in the process. An average taken of this value shows that according to the morphologic measurement the hypertrophied kidney contained 82 per cent of functioning tissue as compared to the amount which existed before the nephrectomy. Measured functionally by means of the ratio  $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c.c. of blood}}$  recovery had progressed to within 79 per cent of the original condition. As is shown in Table 2 of the first section of this paper, no such correlation is shown when the structural change in the kidney is measured by any of the other methods of functional measurement.

#### CONCLUSIONS

1 Hypertrophy of the kidney remaining after a unilateral nephrectomy is most marked in the convoluted tubules.

2 The weight of such a kidney cannot be used to compare the amount of secreting tissue it contains with that contained in a normal kidney, as the normal relations between the secreting portion (convoluted tubule) and the other parts is markedly altered.

3 The relative amounts of secreting tissue in the normal and hypertrophied kidney measured anatomically by means of the cross-section area of the convoluted tubule correlate closely with the functional measurement by means of the ratio  $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c.c. of blood}}$ .

## Book Reviews

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### THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR Pp 1389 Published by the War Department

This is the first of fifteen proposed volumes covering the activities of the Surgeon-General's office during the World War. The purpose of this history is twofold (1) a record of the accomplishments of the Medical Department from an administration standpoint, and (2) a presentation of the various diseases and injuries incident to the War.

This volume is devoted to the administrative function of the Surgeon-General's office.

The first chapter presents a very interesting review of the evolution of the Medical Department in war, beginning with biblical times.

The organization and duties of the various divisions in the Surgeon-General's office is discussed in detail, one chapter being devoted to each of the twenty-six divisions.

The last 700 pages contain the War Department general orders, bulletins, circulars and special regulations.

This volume does not contain much information that is of special interest to the physician in civil life, but it is a valuable historical document.

### FUNFZIG JAHRE NEUROLOGIE By ZWEI VORTRAGE VON PROF CONSTANTIN VON MONAKOW, Direktor des hirnanatomischen Instituts und der Nerven- poliklinik der Universität Zürich Price, Francs 5.50 Pp 100 Zürich, 1924

The author of this booklet has completed fifty years of intensive work in neuropathology and clinical neurology. Living in a small and centrally located country, Switzerland, he has kept in close touch with workers of all countries and avoided the narrowness sometimes present, even in scientists, in large countries. His account of the progress of the anatomy, physiology, and pathology of the brain as well as clinical neurology is therefore based on first hand information, authoritative and vivid.

## STUDIES ON THE METABOLISM OF OBESITY

### I THE RELATION BETWEEN FOOD INTAKE AND BODY WEIGHT IN SOME OBESE PERSONS <sup>†</sup>

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AND

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#### INTRODUCTION

There is a difference, at least in degree, between obesity and overweight. Overweight usually results from overfeeding, sedentary habits or a combination of both. Certain cases of obesity unquestionably follow the same causes, but just as unquestionably other cases of obesity are seen which show neither excessive food intake nor lessened energy expense. In such persons the tendency to accumulate and deposit fat seems to be entirely independent of any of the usual causes of increased weight. Both overeating and underexercise are common faults of mankind, yet excessive obesity is comparatively rare. On the other hand, one sees a fairly large number of healthy but thin persons whose food intake is in excess of their calculated caloric requirements, yet who cannot gain weight under any circumstances. The conclusion seems almost inevitable that the maintenance of body weight may be practically independent of the caloric balance, and that obesity may result from causes other than excessive food intake or diminished energy expense.

To ascertain if possible the cause or causes of "unexplained" obesity prompted us, in 1920, to begin a series of planned metabolic experiments along definite lines. Up to the present time we have studied 1 The food intake of cases of obesity under dietary control 2 The basal metabolism in obesity 3 The specific dynamic effect of various foods <sup>1</sup>

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<sup>†</sup> From the Medical Clinic, the Otto Baer Fund for Clinical Research, and the Nelson Morris Memorial Institute for Medical Research of the Michael Reese Hospital

1 Strouse, Solomon. Carbohydrate Oxidation in Relation to Body Weight, Proc Am Soc for Clinic Investigation, 1921, p 35, Strouse, Solomon, Wang, C C, and Dye, M. The Food Metabolism of Obesity, Proc Inst Med, Chicago 4 169, 1923, Studies on the Metabolism of Obesity Preliminary Report, J A M A 82 2111 (June 28) 1924

The present report deals with the question of food intake in obesity Von Noorden<sup>2</sup> divided obesity cases as follows

1 "Mast-fettsucht" due to *a*, overfeeding, *b*, underwork ("Faulheitsfettsucht"), *c*, a combination of overfeeding and underwork

2 Thyrogenous obesity due to lowered energy exchange *a*, Primary, *b*, secondary, complicated by involvement of other organs like the pancreas, genitalia, hypophysis, etc Later study of the basal metabolism in obesity cast doubt on the thyrogenous origin of von Noorden's Group 2 *b*, or secondary thyrogenous obesity, and most students classify this group as

3 Constitutional obesity This simply means that the person becomes obese not from overeating, underexercise, or hypothyroid disease, but because of a "constitutional" tendency to obesity This, of course, is merely giving a name to an unexplained phenomenon

#### REVIEW OF THE LITERATURE

Recently considerable literature has accumulated on the relation of obesity to diseases of various ductless glands, and in this connection we wish to state that in not a single instance during the four years of this work have we used endocrine terminology in defining obesity Since our work was directed entirely toward a metabolic explanation of obesity, descriptive terms binding the individual case to one or more ductless glands seemed foreign to our purpose In order to obtain objective readings, no clinical interpretation was made on persons sent to the laboratory for study, beyond noting the extent of overweight, and it was not until the laboratory workers had completed and tabulated their results that the clinical notes were consulted and an effort made to correlate the findings The results of this comparative study will be found in a later paper of this series (to be published)

Many cases of so-called constitutional obesity are reported in the literature Von Noorden<sup>3</sup> reports the case of a man aged 39, who weighed 102 kg, and who, exercising freely in the open air, was kept for three months on a diet of 1,720 calories or less and who lost only 1 kg His actual caloric requirements should have been near 2,700 calories A control case weighing 98 kg, exercising less actively, lost 4.8 kg in four weeks on the same diet Von Noorden also reports the case of a woman aged 65, weighing 86 kg, who gained 0.5 kg in six weeks on a diet equivalent to from 900 to 1,000 calories Schwenkenbecher<sup>4</sup>

2 Von Noorden, C Ueber die verschiedenen Formen der Fettsucht, *Med Klin* 5 1, 1909

3 Von Noorden, C Die Fettsucht, Nothnagel's Spezielle Pathologie und Therapie, Vienna, A Holder, 1900

4 Schwenkenbecher Ueber die Ausscheidung des Wassers durch die Haut, *Deutsch Arch f klin Med* 79 29, 1904

studied two obese girls, one of whom began to lose weight only when the food was reduced to 17 calories per kilogram of body weight (total caloric intake, 1,020)

Saloman,<sup>5</sup> in von Noorden's clinic, carefully studied an obese girl, aged 16, who weighed 71.4 kg and who gained 0.5 kg in eight days on a controlled diet of 1,300 calories. During this period she had plenty of open-air exercise. By maintaining the diet at 1,900 calories for some months her weight remained constant.

The more recent and extensive metabolic studies make possible recalculation of figures of earlier work and give a better basis for comparison with normal persons. Du Bois'<sup>6</sup> method of calculating body surface, and the prediction tables of Harris and Benedict,<sup>7</sup> give a standard of comparison now generally accepted as more accurate than any previous standards. In some of the cases quoted here we have recalculated the data to conform to the normal standards of Du Bois or of Harris and Benedict.

Loewy and Hirschfeld,<sup>8</sup> studying the so-called constitutional obesity, report the case of a man, aged 43, weighing 64 kg, height 165 cm, who did "heavy work" for two periods of nine and six days each on diets equivalent to from 2,210 to 2,320 calories containing from 70 to 74 gm of protein. According to the Du Bois standard his basal requirements were 1,620 calories, and his working requirements then should have been a minimum of 2,500 calories. They report a second case of an obese woman, aged 45, who weighed 55 kg and whose height was 149 cm, who kept at work without losing weight for five days on a diet of 1,380 to 1,570 calories. Her basal requirements on the Du Bois scale were 1,328 calories.

Grafe and Graham<sup>9</sup> made a metabolic study lasting 107 days on a young dog, varying the food intake from a hunger period to a long period, during which time the average daily food intake was 210 per cent, the minimum basal metabolism. They found the weight constant "with very slight variations." They quote the old experiment

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5 Saloman. Ueber Durstkuren, Von Noorden's Klinische Abhandlungen **6**, 1905.

6 Du Bois, D., and Du Bois, E. F. A Formula to Estimate the Approximate Surface Area If Height and Weight Be Known, *Arch. Int. Med.* **17** 863 (June) 1916.

7 Harris, J. A., and Benedict, F. G. A Biometric Study of Basal Metabolism in Man, *Carnegie Inst. Wash.*, No. 279, 1919.

8 Loewy, A., and Hirschfeld, F. Beobachtungen ueber das Minimum des Erhaltungsumsatzes. Ein Beitrag zur Frage der sogenannten konstitutionellen Fettsucht, *Deutsch. med. Wchnschr.* **36** 1794, 1910.

9 Grafe, E., and Graham, D. Ueber die Anpassungsfähigkeit des tierischen Organismus an überreichliche Nahrungszufuhr, *Ztschr. f. Physiol. Chem.* **73** 1, 1911.



of Neuman<sup>10</sup> on himself, who, for an almost steady period of two years maintained weight and well-being on diets equivalent to 1,766, 2,199 and 2,403 calories. From their studies Grafe and Graham concluded that caloric intake and energy expense do not always account for the weight curve of human beings.

Grafe and Koch,<sup>11</sup> studying the effect of prolonged overfeeding on metabolism, cited one remarkable instance of weight maintenance despite large variations in caloric intake. A boy, aged 14 years, weighing 26.5 kg, whose height was 140 cm, was kept for ten days on a diet of 88 calories per kilogram of body weight, then fourteen days on 51 calories per kilogram of body weight without any change in the weight curve. This was followed by another ten day period of 40 calories per kilogram of body weight, during which period he lost only 0.5 kg.

Umber<sup>12</sup> claimed to have studied some obese persons for long periods, paying attention to caloric intake, fluid balance and weight, and to have found many such with lowered "energy exchange." He cites the case of an obese woman, aged 61, who weighed 96 kg and whose height was 150 cm (basal metabolism, Du Bois, 1,491 calories daily), who lived on 1,200 gm of milk daily (equal to about 800 calories) for thirty-nine days and who lost only 0.5 kg. Later, for seven days she received 919 calories daily containing 10.3 gm nitrogen. She gained 7.2 gm nitrogen, but her weight remained at 96 kg, which means that she maintained body weight on 9.6 calories per kilogram of body weight. Umber also reports a case which, from the clinical description (no basal metabolism study) belonged to the group of hypothyroids. A woman, aged 45, weight 97.7 kg, height 163 cm (basal metabolism, Du Bois, 1,815 calories), who for twelve days had the equivalent of 1,000 calories, for six days 800 calories and who remained in nitrogen balance and maintained weight. He reports a third case of apparently hypophyseal obesity in a boy, aged 12, weight 96 kg, height 156 cm (basal metabolism, Benedict and Talbot,<sup>13</sup> 1,850 calories), who kept his weight on 1,600 calories.

During's<sup>14</sup> studies led him to believe that, in constitutional obesity, loss of weight paralleled water and salt excretion, an opinion shared

10 Neuman, R. O. *Arch f Hyg* 45 1, 1902, quoted by Grafe and Graham.

11 Grafe, E., and Koch, R. *Ueber den Einfluss langdauernder starker Uebernahrung auf die Intensitat der Verbrennungen im menschlichen Organismus* (Untersuchungen bei Mastkuren), *Deutsch Arch f klin Med* 106 564, 1912.

12 Umber. *Konstitutionelle Fettsucht und innere Sekretion*, *Med Klin* 9 2014, 1913.

13 Benedict, F. G., and Talbot, F. B. *Metabolism and Growth from Birth to Puberty*, *Carnegie Inst Wash No* 320, 1921.

14 During, M. *Ueber Storungen des Flussigkeits und Salzgleichgewichts bei gewissen Fallen der sogenannten "konstitutionellen Fettsucht,"* *Cor-Bi f schweiz Aerzte* 44 1425, 1914.

by Grafe<sup>15</sup> Grafe studied several cases in which no loss of weight occurred, even following the intake of food of very low caloric value

Talbot<sup>16</sup> studied the metabolism of a very obese child with a small sella turcica and gives the following figures A boy, aged 2 years and 9 months, weighed 24.8 kg, whose height was 94 cm, body surface was 0.879 sq cm The average daily caloric intake for three weeks was 895 and the child gained weight The normal requirement as figured by Talbot, was 1,200 calories On from 700 to 800 calories the child lost weight His basal metabolism varied from 1,046 calories when awake to 677 when asleep It was minus 41 per cent compared to age, and minus 32 per cent compared to weight

Rahe and Plaut,<sup>17</sup> studying the effect of food poor in protein, report the case of a man aged 40 of normal build, who weighed 67 kg and whose height was 168 cm, who on a diet of between 1,000 and 1,300 calories, gained 5 kg in nineteen days (basal metabolism on the Harris and Benedict tables is 1,558 calories) This followed a period of under-nutrition, and may be explained on the basis of the lowered metabolism which has been found to follow such periods

#### EXPERIMENTAL DATA

From this review of the available literature it is apparent that obesity can and does occur in persons without showing any direct relation to food intake Our own experience had led us to believe that underweight in otherwise healthy persons also occurs even when the caloric intake is more than sufficient to supply energy demands Speaking metabolically, the "constitutional" obese and the healthy underweight may represent extremes of the same problem

#### REPORT OF CASES

CASE 1—Our first experiment was a clinical test on a very thin, healthy man, aged 39, weighing 52 kg, and whose height was 175 cm He was a very active worker, a physician, who ate normal food and slept from six to seven hours out of the twenty-four On a four weeks' vacation he increased his food intake approximately 50 per cent, mainly in carbohydrates, he slept from ten to fourteen hours a day, took no violent exercise, and spent most of the time lying on a hammock on the porch engaged in reading current nonmedical magazines and novels Although excessively fatigued at the beginning of the vacation and decidedly refreshed at the end of the four weeks, his weight

15 Grafe, E Zur Pathologie und Therapie der sogenannt "konstitutionellen Fettsucht," *Deutsch Arch f klin Med* **133** 41, 1920

16 Talbot, F B The Metabolism of a Very Obese Child with a Small Sella Turcica (Typus Frolich?), *Am J Dis Child* **20** 331 (Oct) 1920

17 Rahe, F, and Plaut, R Zur Frage Erweiss-arter Ernährung, *Deutsch Arch f klin Med* **137** 187, 1921

remained constant Surely if his weight were dependent on the caloric equation, the four weeks of overfeeding and underexercise, coupled with the removal of the nervous activity of his vocation, should have resulted in a gain of weight

CASE 2—A young woman, aged 30, whose height was 165 cm, and whose weight was 86.8 kg, the subject of much of our first two years' work was very eager to cooperate and very reliable She had a scale at home, to the use of which she was accustomed through feeding her diabetic mother All articles of food were weighed and noted in a book from which the food values were subsequently calculated by us She had been obese for years and showed other signs of supposed endocrine disturbance (amenorrhea, hair on face) She said that she was a very light eater, and all her life she had been a hard worker At the time of the experiment she "kept house" for the family, doing all the cooking, cleaning, and general housework including floor scrubbing, in addition

TABLE 1—*The Weight and Calories of Case 2*

Date	Calories	Weight, Kg	Date	Calories	Weight, Kg
9/ 2/21	849	86.8	12/21/21	593	
9/ 3/21	1,131		12/22/21	565	
9/ 4/21	1,116		12/23/21	888	
9/ 5/21	1,658		12/24/21	837	
9/ 6/21	690		12/25/21	974	
9/ 7/21	669		12/26/21	695	
10/24/21	803	83.7	12/27/21	489	
11/27/21	1,672	84.1	1/10/22	2,143*	
12/19/21	1,097		1/11/22	1,742	
12/20/21	1,088		1/12/22		85.6

\* Candy spree

TABLE 2—*Case of Girl With Appearance of Gigantism*

Date, 1923	Diet				Urine Nitrogen	Weight, Kg
	Protein	Fat	Carbohydrate	Calories		
September 20	98	98	150	1,874		104.5
September 21	84	94	150	1,782		
September 22	85	107	98	1,695		105
September 23	84	91	134	1,691		
September 24	82	90	110	1,578	13.6	104.5
September 25	81	101	111	1,687	13.6	
September 26	84	108	124	1,804	12.3	105
September 27	89	127	128	2,011	13.1	
September 28	88	91	129	1,687	8.4	104.5
September 29	82	108	125	1,606	14.3	
September 30	90	75	90	1,395	12.6	103.1
October 1	89	71	83	1,347	15.8	
October 2	89	76	90	1,395	16.9	104
October 3	88	74	79	1,334	16.5	
October 4	89	76	90	1,395	17.6	
October 5	90	75	90	1,395	12.8	106

to acting as nurse and dietician for her diabetic mother Previous notes on her food intake seemed to indicate such a low caloric value as to make a weighed dietary study of particular interest Basal metabolism 1,526 calories

It will be noted that, except for the two days of her candy spree, the calculated dietary periods were considerably under her basal metabolic requirements These periods represent no special time, but are typical of the food she took as an average diet while at hard labor It should be recalled here that statistics on heart disease show that from the standpoint of incidence of heart disease, the "housework" of the woman without domestic help places her in the same class as the laborer The very slight changes in the weight curve are also typical of what the patient had found out for herself, that her weight did not depend on the amount of food she ate

CASE 3—A girl, aged 15, who weighed 105 kg, with the appearance of gigantism, whose height was 177 cm, had basal metabolism of 1,844, 4.6 per cent

below normal of 1,933, was under hospital observation for a period of sixteen days on a weighed diet. At no time during the study was the patient confined to her bed, but she was allowed the freedom of the floor. Careful observation convinces us that she ate no more than was indicated by the figures. Almost every day food was returned, and the chart indicated the only food eaten. It will be seen that she maintained her weight for sixteen days on a diet considerably below her basal requirements, and at the end of the experiment weighed 1.5 kg. more than at the beginning.

CASE 4—R. K., a woman, aged 26, whose weight was 78.3 kg., and whose height was 148.5 cm., had been under our observation for several years and

TABLE 3—*Obese Woman With Vaginal Bleeding*

Date, 1923	Pro- tein	Fat	Carbohy- drate	Calories	Urinary Nitro- gen	Weight		Vaginal Bleed- ing	Medication
						Lb	Kg		
11/19	56	51	101	1,063	18.03	167	76	—	Desiccated thyroid, $\frac{1}{2}$ grain, desic- cated whole pituitary, 1 grain, corpus luteum, 5 grains, three times daily by mouth
11/20	50	50	100	1,050	7.45			—	
11/21	50	49	99	1,037	7.64			0	
11/22	51	49	100	1,055	10.56	165	75	0	
11/23	50	50	101	1,054	8.91			0	
11/24	50	50	101	1,054	8.5			+	Desiccated whole pituitary, 1 grain corpus luteum, 5 grains, three times daily by mouth
11/25	50	50	100	1,056	6.9			—	
11/26	50	50	100	1,050	4.65	162	73.7	+	
11/27	51	50	101	1,058	2.68			+	
11/28	50	50	101	1,054	8.81			0	
11/29	50	50	99	1,046	8.85	161.5	73.5	—	Obstetric pituitary extract hypo- dermically daily *
11/30	51	51	100	1,063	6.60			—	
12/ 1	51	51	100	1,063	6.13			+	
12/ 2	51	50	101	1,058	5.88			—	
12/ 3	50	51	100	1,059	7.97	160	72.8	+	
12/ 4	49	50	100	1,046	10.45			+	Obstetric pituitary extract, corpus luteum, hypodermically daily *
12/ 5	50	50	100	1,050	11.53			0	
12/ 6	47	29	86	793		161	73.4	—	
12/ 7	49	33	95	873				+	
12/ 8	50	50	100	1,050	8.29			+	
12/ 9	50	51	100	1,059	9.51			+	Desiccated thyroid 1 grain three times daily by mouth
12/10	50	51	100	1,059	7.15	157.5	71.6	0	
12/11	50	50	100	1,050	11.33			0	
12/12	50	50	100	1,050	8.37			0	
12/13	50	50	100	1,050	7.87	156	71	0	
12/14	50	50	100	1,050		155.5	70.7	0	
12/15	52	50	100	1,058				0	

\* Size of ampule used, 1 cubic centimeter

TABLE 4—*Case of Woman Given to Overeating*

	Calories	Weight	
		Lb	Kg
11/2/21	564	151.5	68.8
11/3/21	427		
11/4/21	750		
11/5/21	720		
11/6/21	885		
11/7/21	477		
11/8/21	523	148.5	67.5

always maintained a steady weight on a low caloric diet. She was admitted to the hospital in November, 1923, because of excessive vaginal bleeding for which no local cause could be found. Because of difficulty in keeping her in the hospital without treatment, the dietary study is complicated by the administration of various glandular extracts. Her basal metabolism was 1,934, her activities in the ward should have raised her energy requirements approximately 30 per cent. For a period of one month her diet was approximately 1,050 calories, 84 per cent less than her basal requirements, more than 100 per cent less than her calculated needs. The weight curve (Table 3) shows a loss of 1 kg. during

the first four days, then a practically steady curve for fifteen days, followed by a more definite loss during an eight day period of thyroid feeding (desiccated thyroid, 3 grains daily)

CASE 5—A perfectly healthy "stout" woman, frankly given to overeating and underexercising, with a normal basal metabolism, wished to be reduced

The interesting feature in this patient lies in the very low caloric intake necessary to reduce her weight 13 kg in eight days. Metabolism studies showed perfectly normal metabolism at the beginning and end of the experiment, except that the respiratory quotient, after the eight days of subcaloric diet, indicated oxidation of body fat. This of course was to be expected under the conditions of the experiment

#### SUMMARY

1 The literature on obesity is reviewed to prove the existence of an entity, which for want of a better name is called constitutional obesity

2 Persons showing this predisposition show no interdependence between food intake, energy expense and weight

3 Dietary studies of some new cases are given, also a clinical study of a healthy, very thin man is given

4 The data thus accumulated definitely prove that certain types of obese persons maintain their weight without regard to the usually accepted caloric balance

# STUDIES ON THE METABOLISM OF OBESITY

## II BASAL METABOLISM \*

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In the first communication we showed both by quotations from the literature and by our experiments that certain obese persons maintained body weight on diets below their calculated caloric requirements <sup>1</sup> To explain this apparent anomalous balance between caloric intake and energy expense, we made an intensive study of the specific dynamic action of foods in persons of widely varying body build The results of this study will be published shortly A rather large and interesting series of basal metabolism readings were accumulated during this research, and since the subject of the basal metabolism in obesity cannot be considered closed we present in this paper our data on the basal metabolism in obesity

### REVIEW OF THE LITERATURE

Before the development of modern methods of studying gaseous exchange and the accumulation of more accurate standards of comparison, the literature on the metabolism of obesity contains much conjecture and a few isolated studies In 1897 Magnus-Levy <sup>2</sup> studied the basal metabolism of fourteen cases of obesity, and found no change except in myxedema, in which condition he found lowered basal metabolism Jaquet and Svenson, <sup>3</sup> in 1900, suggested that variations in basal metabolism could not explain the metabolic anomaly in obesity, and predicted that study of the twenty-four hour metabolism, including the effect of muscular work, would be necessary They studied the basal metabolism of three cases in which a normal rate was found

In 1907 von Noorden <sup>4</sup> speaks of "corpulency due to a slowing in the processes of metabolism" but was able to report only twenty-four

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\* From the Otto Baer Fund for Clinical Research, and the Gusta Morris Rothschild Fund of the Michael Reese Hospital and the Nelson Morris Institute for Medical Research

1 Strouse, Solomon, and Dye, M Studies on the Metabolism of Obesity 1 The Relation Between Blood Intake and Body Weight on Some Obese Persons, Arch Int Med **34** 267 (Sept) 1924

2 Magnus-Levy, A Untersuchungen zur Schilddrusenfrage, Ztschr f klin Med **3** 269-1897, Der Einfluss von Krankheiten auf den Energiehaushalt im Ruhezustand, Ztschr f klin Med **60** 177, 1906

3 Jaquet, A, and Svenson, N Zur Kenntnis des Stoffwechsels fettsuchtiger Individuen, Ztschr f klin Med **41** 375, 1900

4 Von Noorden, C Obesity Metabolism and Practical Medicine, Anglo-American Edition, Chicago, W T Keener & Co, 1907, Vol 3

studies of the respiratory exchange, "the whole of the existing records" Von Noorden criticized the correctness of these readings on various technical grounds. Studies of Loewy and Hirschfeld<sup>5</sup> on three obese persons forced them to conclude that, up to their time, no one had proved "lowered energy exchange" in obesity. In 1915 Means<sup>6</sup> again studied the question. He showed that the basal metabolism in two cases of "simple obesity," figured per square meter and by the hour, using the Du Bois formula, was normal, in one case of "hypopituitarism" it was increased, in two other cases (hypopituitary?) it was low. One year later Means<sup>7</sup> says "there is no characteristic change whatsoever in the basal metabolism even in very extreme cases of obesity." Occasionally he noted a slight reduction when clinical evidence of disturbed internal secretion was present. His study embraced twelve cases.

Haussleiter<sup>8</sup> also studied twelve cases and concludes that there are three types of obesity:

TABLE 1—*Findings in Haussleiter's Case*

Case	Age	Sex*	Weight, Kg	Height, Cm	Haussleiter Basal Metabolism	Du Bois Predicted Basal Metabolism
1†	13					
2	13		67.4	156	2,237	1,992
3	13	♀	69.0	151	1,240	1,879
4	32	♂	79.65	167	2,082	1,810
5	36	♂	88.5	168	2,880	1,906
6‡						
7	10	♀	38.0	141	1,465	1,193
8	18	♂	64.0	144	1,630	1,272
9	34	♀	83.5	154	1,910	1,594

\* In this column ♀ indicates female, ♂ male

† Cardioresenal disease with edema

‡ Oxygen consumption so high that it must be abnormal

1 Endogenous obesity, with increased basal metabolism

2 Endogenous obesity with periodic variations of basal metabolism on the lower border of the normal

3 Endogenous obesity (thyrogenous form), with basal metabolism absolutely lower than the lowest normal

A careful review of the work of Haussleiter, on the basis of our large experience with metabolic studies on obese persons, forces us to suspect that his experimental conditions could not have been perfect

5 Loewy, A, and Hirschfeld, F. Beobachtungen uber das minimum des Erhaltungsumsatzes. Ein Beitrag zur Frage der sogenannten konstitutionellen Fettsucht, Deutsch med Wchnschr **36** 1794, 1910

6 Means, J. H. Studies of the Basal Metabolism in Obesity and Pituitary Disease, J. M. Res. **32** 121, 1915

7 Means, J. H. The Basal Metabolism in Obesity, Arch. Int. Med. **17** 704 (May) 1916

8 Haussleiter, H. Ueber den Gaswechsel verschiedener Formen von Fettsucht und seine Beeinflussung durch Nahrungsaufnahme, Arbeit und Arzneimittel, Ztschr. f. exper. Path. u. Therap. **17** 413, 1915

Some of his basal readings recalculated on either DuBois' scale, or according to the Benedict-Harris prediction tables, and compared to the large recent accumulations of normal belong to the group now associated almost entirely with hyperactivity of the thyroid gland

Because of the difference in the results of Haussleiter's studies and those reported by most other workers, it seems wise to report his cases in more detail

Talbot<sup>9</sup> reported one very obese child, aged 2 years and 9 months, with Frolich's syndrome, who showed a basal metabolism 41 per cent below normal compared to age and 32 per cent compared to weight

In the large series of normal cases that Benedict and Carpenter<sup>10</sup> studied, are found some with height and weight relationship varying more or less from normal, but the variations in basal metabolism found in their series bear no direct relationship to the body build. For instance, their tallest and thinnest man showed a basal metabolism of 34.9 calories per square meter per hour, their shortest and stoutest subject showed 35.2 calories per square meter per hour, and the variations in apparently normal human beings were from 33.9 to 44.2 calories per square meter and hour

Grafe,<sup>11</sup> in 1920, expressed the belief that most cases of obesity are not pure expressions of either exogenous or endogenous causes, although one or the other is predominant in each case. His studies on basal metabolism showed great variations

Plaut<sup>12</sup> studied a large series of normal, obese, and constitutionally thin persons, and found a normal basal metabolism in all cases of obesity except in myxedema and thyrogenous obesity, in which the basal metabolism was lowered. In 1923<sup>12</sup> she added twenty-six more cases, and arrived at the same conclusion

#### EXPERIMENTAL DATA

Our own studies on basal metabolism were incidental to more extensive investigations of the specific dynamic action of foods in cases of obesity. During the season from 1920 to 1921 all the work was done with a Benedict portable respiration apparatus<sup>13</sup>. During this year

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9 Talbot, F. B. The Metabolism of a Very Obese Child with a Small Sella Turcica (Typus Frolich), *Am. J. Dis. Child* **20** 331 (Oct) 1920

10 Benedict, F. G., and Carpenter, T. M. Food Ingestion and Energy Transformations, Carnegie Inst. Wash., No. 261, 1918

11 Grafe, E. Zur Pathologie und Therapie der sogenannten konstitutionellen Fettsucht, *Deutsch. Arch. f. klin. Med.* **133** 41, 1920

12 Plaut, R. Gaswechseluntersuchungen bei Fettsucht und Hypophysenkrankungen, *Deutsch. Arch. f. klin. Med.* **139** 285, 1922, *ibid.* **142** 266, 1923

13 Some of this year's work was performed in the laboratory of Home Economics of the University of Chicago, with the active guidance of Prof. Katherine Blunt



repeated readings were made on a somewhat small group of persons, including both sexes, and of body build varying from extreme thinness in healthy persons to cases of marked obesity. The usually accepted technic was adopted. The subject not having eaten for from twelve to fifteen hours previously, rode to the laboratory, and was given a rest period of at least thirty minutes before the test was started. Basal metabolism was figured entirely on oxygen consumption. Since the fall of 1921, all work has been done with the Tissot gasometer, the gas analyses being made with the Haldane apparatus. The cases are grouped in tables of normal, underweight and overweight subjects, as

TABLE 2—Results with the Benedict Apparatus

Subject	Date	Sex*	Age	Height, Cm	Weight, Kg	Devia- tion from Normal, per Cent	Heat Production					
							Calories per 24 Hours			Calories per Sq M per Hour		
							Ob served	Harris Benedict Predic- tion	Differ- ence, per Cent	Ob- served	Du Bois For- mula	Dif- ference per Cent
Normal Subjects												
1 P	2/25/21	♀	27	150.5	51	+6	1,190	1,296	-8.9	37.2	37.0	+0.54
2 M	2/1/21	♂	38	176	79.5	+8	1,850	1,784	+3.7	38.9	39.5	-1.52
3 L	3/1/21	♀	25	165	61	0	1,600	1,426	+12.1	40.5	37.0	+9.5
Underweights												
4 S	1/17/21	♂	38	174	51	-28	1,510	1,382	+9.2	39.3	39.5	-0.52
4 S	1/27/21	♂	38	174	51	-28	1,510	1,382	+9.2			
5 P	3/18/21	♀	23	170	52	-17	1,352	1,359	0	35.3	37.0	-4.6
6 D	3/16/21	♂	25	170	59	-11	1,670	1,560	+7.1	41.2	39.5	+4.3
7 K	3/15/21	♂	25	182	61.4	-19	1,450	1,633	-12.3	33.7	39.5	-14.7
8 Ka	3/23/21	♀	30	157	50	-12	1,245	1,283	-2.9	35.1	36.5	-3.8
7 K	1/26/22	♂	26	182	61.4	-20	1,540	1,633	-6.8	35.2	39.5	-10.9
7 K	2/9/22	♂	26	182	61.4	-20	1,510	1,633	-8.7	35.0	39.5	-14.0
4 S	2/7/22	♂	39	174	51	-28	1,425	1,382	+2.9	37.1	39.5	-6.1
Overweights												
9 F S	1/28/21	♀	27	165	85	+43	1,810	1,647	+9.9	39.5	37.0	+6.8
10 G	2/7/21	♀	32	153.5	71.5	+29	1,395	1,472	-5.5	34.2	36.5	-6.8
9 E S	10/25/21	♀	28	165	83.6	+40.5	1,525	1,628	-6.3	33.4	37.0	-9.7
9 F S	11/28/21	♀			84.1	+41.5	1,685	1,633	+3.2	36.5	37.0	-0.5
9 E S	1/12/22	♀			85.5	+43.7	1,815	1,647	+10.2	39.2	37.0	+5.9
9 F S	3/8/22	♀			86.3	+45.0	1,713	1,634	+3.6	36.8	37.0	-0.5
9 F S	6/1/22	♀			85.5	+43.7	1,634	1,647	-0.79	35.3	37.0	-4.6
11 Kau	3/17/21	♀	35	157	79	+35	1,280	1,538	-18.2	29.7	36.5	-18.6
12 Kar	3/23/21	♂	35	163	70.5	+13.5	1,475	1,612	-8.5	34.9	39.5	-11.6
13 S	3/27/21	♀	39	177	127	+78	1,860	2,014	-7.7	33.0	36.5	-9.6

\* In this column, ♀ indicates female, ♂ male

determined by comparison with the standards accepted by life insurance companies<sup>14</sup>

Our results are given in Tables 2 and 3 and are graphically arranged in Chart 1. Table 2 contains the work done with the Benedict portable apparatus, Table 3 that done with the Tissot gasometer. It will be noted that body weight is the only "standard" we use and that our subjects varied from 30 per cent underweight to 140 per cent overweight. No attempt is made at this time to make clinical groupings, our sole object was to obtain objective metabolic data on overweight regardless of the cause.

14 Association of Life Insurance Medical Directors and Actuarial Society of America, Medico Actuarial Mortality Investigation, 1912

All mathematical calculations of heat production are made on the basis of the Harris-Benedict prediction tables, and from the height-weight formula for body surface of Du Bois<sup>15</sup> excepting in the case of a child, aged 12 years (Subject 30, Table 3), whose metabolism

TABLE 3—Results with the Tissot Gasometer

Subject	Date	Sex*	Age	Height, Cm	Weight, Kg	Deviation from Normal, per Cent	Heat Production					
							Calories per 24 Hours			Calories per Sq M per Hour		
							Observed	Harris-Benedict Prediction	Difference, per Cent	Observed	Du Bois Formula	Difference, per Cent
Normal Subjects												
14 M S	4/12/23	♀	21	167.5	62.3	-3.0	1,403	1,463	-4.1	34.4	37.0	-7.0
14 M S	5/16/23			167.5	61.4	-1.5	1,477	1,453	+1.6	36.4	37.0	-1.7
15 M W	10/ 8/23	♀	24	160	55.5	-0.8	1,455	1,369	-6.3	38.6	37.0	+4.3
15 M W	11/ 1/23			160	55	-1.6	1,455	1,369	+6.6	38.8	37.0	+4.9
16 D K	10/18/23	♀	22	164.5	57.8	+0.8	1,241	1,408	-4.8	34.3	37.0	-7.3
16 D K	11/14/23				58.2	-1.5	1,383	1,409	-1.9	35.4	37.0	-4.4
16 D K	12/18/23				58.0	-1.2	1,296	1,411	-8.2	33.0	37.0	-10.9
16 D K	12/21/23				58.6	0	1,418	1,417	+0.1	36.0	37.0	-2.8
Underweight												
17 M A	3/15/23	♀	25	166.2	47.3	-22.4	1,120	1,298	-13.7	30.0	37.0	-16.2
17 M A	4/ 9/23			166.2	47.3	-22.4	1,181	1,298	-9.0	32.6	37.0	-11.9
18 B M	3/26/23	♀	31	170	47.3	-27.8	1,313	1,276	+2.9	35.8	36.5	+2.0
19 C T	11/19/23	♀	26	159.5	46.4	-22.5	1,415	1,274	+9.6	40.1	37.0	+9.7
20 B D	2/23/24	♀	21	159.4	41.6	-25.6	1,265	1,249	-1.3	38.2	37.0	+3.3
20 B D	3/ 4/24	♀	21	159.1	41.5	-25.6	1,172	1,248	-6.1	35.4	37.0	-4.2
20 B D	3/10/24	♀	21	158.8	41.6	-25.6	1,161	1,249	-7.0	35.1	37.0	-5.2
4 S	2/28/24	♂	42	173.4	50.2	-20.8	1,367	1,341	+1.9	35.9	38.5	-6.7
Overweight												
21 M L	10/22/22	♀	26	152.5	95.8	-70.1	1,896	1,637	+12.4	41.4	36.5	+13.4
22 S T	10/14/22	♀	17	160	91	-66.7	1,691	1,740	-2.9	36.5	40.0	-8.7
22 S T	11/11/22				90	+65	1,537	1,732	-11.3	33.2	40.0	-17.0
22 S P	2/ 5/23	♀	27	157.5	100.4	-81.1	2,168	1,783	+21.6	45.1	37.0	+21.9
24 R K	2/26/23	♀	26	148.5	76.4	+44.8	1,726	1,537	+12.3	42.3	37.0	+14.3
24 R K	5/ 8/23				78.3	-49.4	1,934	1,555	+24.4	46.9	37.0	+26.7
25 M N	4/16/23	♀	29	155	93.6	+71.6	1,391	1,702	-18.2	30.0	37.0	-18.9
9 L S	4/27/23	♀	24	165	118.1	+91.2	2,546	1,931	+31.7	47.9	36.5	+31.2
9 F S	5/ 8/23				117.8	-91.1	2,289	1,927	+18.8	43.2	36.5	+18.4
26 S A	5/24/23	♀	25	149.5	82.3	-55.6	1,563	1,600	-2.3	36.9	37.0	-0.3
26 S A	6/ 6/23				80	-51.7	1,728	1,578	+9.5	41.2	37.0	+11.4
27 G P	6/12/23	♀	24	163.8	101.2	-63.9	1,915	1,766	-8.4	38.8	36.5	+6.3
27 G P	7/11/23				101.2	-63.9	1,664	1,766	-5.7	36.1	36.5	-1.1
28 M S	6/19/23	♀	33	159.5	137.3	+136.1	2,339	2,110	-10.8	42.4	36.5	+16.4
28 M S	8/14/23				140	+140.6	2,119	2,125	-0.7	38.4	36.5	+5.2
29 A D	7/24/23	♂	16	169.5	84.6	-37	1,929	1,969	-2.0	41.1	43.0	-4.1
29 A D	7/31/23				83.7	+35	1,706	1,969	-12.3	36.9	43.0	-14.2
29 A D	8/ 7/23				82.2	-33	1,763	1,937	-8.9	38.3	43.0	-10.9
30 E M	8/28/23	♀	12	160.5	97.8	+92.0	1,929	1,828	+5.2	41.1	40.0	+2.8†
										44.7		+8.1‡
30 E M	9/15/23			161.5	98.6	+90.3	2,035	1,828	+10.7	42.0	40.0	+5.0†
										44.7		+6.0‡
30 F M	9/24/23			161.5	100	+92.9	1,906	1,851	+7.8	41.0	40.0	+2.5†
										44.7		+8.3‡
31 R K	12/13/22	♀	27	149.9	75	+43	1,475	1,528	-3.5	35.9	37.0	-3.0
32 P	1/ 9/24	♀	32	171.1	103.1	+58	1,726	1,893	-4.5	33.5	36.5	-8.3

\* In this column, ♀ indicates female, ♂ male

† Based on Benedict-Talbot calculations

‡ Based on Du Bois formula

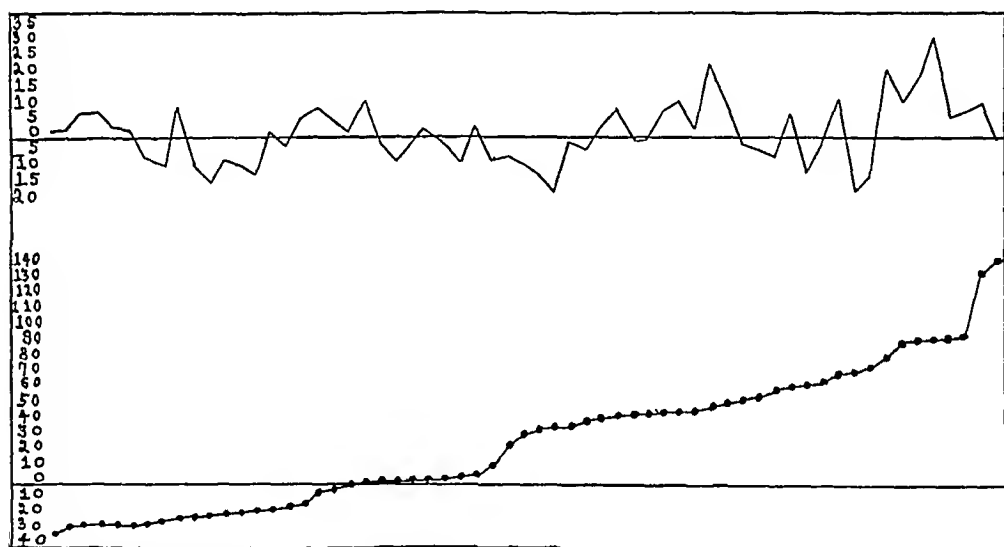
was calculated from Benedict and Talbot's studies<sup>16</sup> The results are thus presented in two forms, and except in the child, aged 12 years, it

15 Carpenter, T M Tables, Factors and Formulas for Computing Respiratory Exchange and Biological Transformations of Energy, Carnegie Inst Wash No 303, 1921

16 Benedict, F G, and Talbot, F B Metabolism and Growth from Birth to Puberty, Carnegie Inst Wash No 302, 1921

is quite interesting to note how closely the two methods of calculation approximate each other even with the widely varying types of persons studied<sup>17</sup> Otherwise the tables require no comment

In the chart we have drawn two curves, the lower one a weight curve showing the deviation from normal of each person, and plotted as an ascending line from the lowest weight (minus 30 per cent) to the highest (plus 140 per cent) In the upper curve the variation of each person from his normal basal metabolism (Harris-Benedict prediction) is correspondingly plotted It can be seen at a glance that there is no direct or constant association between the weight variation of any one individual and his basal metabolism All three groups show basal metabolic rates above and below the zero line, the majority being between



Results of basal metabolism experiments Lower curve shows the deviation in weight from normal of each person Upper curve shows the variation of each person from the normal basal metabolism

plus and minus 10 per cent If we pick out for study the few cases which go beyond these limits, we find that Subject 11, Table 2 (minus 18 per cent) showed some clinical signs of myxedema Subject 25, Table 3 (minus 18.3 per cent) had been operated on, both ovaries had been removed

Subject 24, Table 3 (plus 24.4 per cent) was receiving thyroid extract at the time the test was made On a previous occasion, she had shown a basal metabolic rate of plus 12 per cent

Subject 23, Table 3 (plus 21.6 per cent) was a case of subacute polyarthritis with obesity On a previous test she had shown a basal

<sup>17</sup> Means, J. H., and Woodwell, M. N. Remarks on the Standards of Normal Basal Metabolism, *Arch Int Med* 27:608 (May) 1921

metabolic rate of plus 12 per cent. The infection of the joints may have increased her rate.

Subject 9, Table 2 (plus 31.7 per cent and plus 18.8 per cent) had a large goiter, with tachycardia, nervousness and tremendous gain in weight. The thyroid gland was removed, which on section showed a colloid goiter with multiple small adenomas.

#### SUMMARY AND CONCLUSION

Sixty-one observations on basal metabolism were made on persons of different weight and build. These observations include eleven on six normal, seventeen on nine underweight and thirty-three on seventeen overweight subjects.

From this study it can be stated that neither excessive underweight nor excessive overweight is associated with a constant change in basal metabolism.

We therefore conclude with the statement that obesity cannot be caused by changes in the basal metabolism.

# A COMPARATIVE STUDY OF THE PHENOLTETRACHLORPHTHALEIN AND HEMOCLASTIC TESTS OF LIVER FUNCTION\*

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AND

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The early diagnosis of hepatic disease and of the type of lesion present is of the utmost importance. A slight enlargement of the liver with or without symptoms, or the occurrence of a group of symptoms pointing to hepatic disturbance, is not an uncommon finding. There are also some obscure abdominal conditions, in which even the diagnosis of the organ affected cannot be made conclusively. In all these cases a practical test of the liver function is a most welcome help in solving the problem.

Many clinical procedures have been described for detecting deranged hepatic function. The majority are based on one or more of the functions attributed to the organ, but up to the present time few, if any, have been able to withstand a careful scrutiny.

In 1909, Abel and Rowntree,<sup>1</sup> searching for an intravenous cathartic, noticed that when phenoltetrachlorphthalein was injected into experimental animals, most of the dye was excreted by the liver and recovered in the feces unchanged. Further studies by other investigators confirmed their results, and indicated the possible value of the dye in detecting hepatic dysfunction. Considerable work was done by measuring the percentage of dye that could be recovered either from the feces or from the duodenal contents. The inaccuracy of these methods is evident, and it is due to this fault that the dye test did not receive the clinical and experimental study that it deserved.

Since Rosenthal<sup>2</sup> devised his new technic for the colorimetric estimation of the dye in the blood plasma, many of the errors of the older method can now be prevented. Rosenthal found that by intravenous injection of 5 mg of phenoltetrachlorphthalein per kilogram of body weight, from 2 to 6 per cent of the dye could be detected in the blood plasma of normal persons after fifteen minutes, and practically none at the end of one hour. In cases of liver disease, high percentages may be

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1 Abel and Rowntree. *J Pharmacol & Exper Therap* **1** 231, 1909.

2 Rosenthal, S M. A New Method of Testing Liver Function with Phenoltetrachlorphthalein, *J A M A* **79** 2151 (Dec 23) 1922.

found several hours after injection of the dye. The test is one of the newest additions to our already loaded diagnostic equipment, and unless it proves of decided value it will be condemned to perish like the Cambridge and similar reactions, which are now slowly passing into the archives of medical history.

Another most interesting and promising of these new hepatic tests is founded in what Widal, Abrami and Iancovesco<sup>3</sup> call the "proteopexic" function of the liver. From experiments on animals with a modified Eck fistula, they found that the introduction of proteose substances into the systemic circulation so disturbed the colloidal balance of the blood, as to produce a complex reaction of constant character. They were able to duplicate their results by feeding proteins to animals with experimentally damaged livers. This indicated that the complex was dependent on the inability of the liver to perform its normal physiologic action on the digested proteins. This complex, called the "hemoclastic reaction," is manifested by a lowering of the blood pressure, hypercoagulability of the blood, decreased refractive index of the blood serum and leukopenia.

In the normal animal with intact liver, the results are correspondingly reversed, namely, rise of the blood pressure, hypocoagulability of the blood, increased refractive index of the blood serum and leukocytosis. As suggested by the authors the leukocytic factor being the most constant and easiest to determine, is the one to which especial attention should be paid. Feinblatt<sup>4</sup> tested eighty clinically normal medical students and in not one single instance did he fail to get a leukocytosis after ingestion of a protein. Andreen-Svedberg,<sup>5</sup> of Stockholm, found leukopenia to follow ingestion of protein in sixteen cases of undoubted hepatic disease. This test has been studied much more frequently in Europe than in this country. One group of investigators has suggested that it represents a vague reflex and as such has no clinical value, or that the leukopenia is only constant with "vagotonic functional neuroses." It has also been criticised in that it varies from day to day and represents merely a different distribution of the leukocytes.

In the present work a comparative study was made of the phenol-tetrachlorophthalein and hemoclastic tests on cases of known or suspected liver disease. When possible, the pathologic changes of the organ were examined either at the operating table or at necropsy. A few cases of minor extrahepatic ailments were examined as controls.

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<sup>3</sup> Widal, F., Abrami, P., and Iancovesco, V. *Presse méd* **28** 893 (Dec 11) 1920.

<sup>4</sup> Feinblatt, H. M. *Alimentary Leukocytosis in Eighty Normal Men*, *J A M A* **80** 613 (March) 1923.

<sup>5</sup> Andreen-Svedberg, A. *Hygiea, Stockholm* **85** 115 (Feb 28) 1923.

## METHODS

*Phenoltetrachlorophthalein Test*—The technic of Rosenthal<sup>2</sup> was used, with slight modifications. A solution was made of which 1 c c contained 20 mg of the dye. The patient was weighed and the calculated amount for the sterile dye (5 mg per kilogram of body weight) was drawn into the syringe. From a vein in one arm 10 c c of blood was withdrawn with an appropriate needle. Through the same needle the dye was immediately injected. The need of washing the dye in with a sterile saline solution was not apparent. From a vein in the other arm, approximately 5 c c samples of blood were withdrawn at intervals of fifteen minutes, one hour and three hours, providing there was a retention at the end of the first hour. The bloods were centrifuged and the plasmas separated. To each was added one drop of 5 per cent sodium hydroxid for each cubic centimeter of plasma. Assuming an alkaline solution of the dye containing 10 mg per hundred cubic centimeters to be 100 per cent, a set of solutions was made consisting of 100, 80, 60, 40, 20 and 12 per cent respectively. To small test tubes with equal diameters were added 0.2 c c portions of each of these solutions, and 0.6 c c of the plasma taken before the injection of the dye. This set of standards, containing respectively 25, 20, 15, 10, 5 and 3 per cent was used in reading the unknown plasmas, 0.8 c c portions of the alkalinized plasmas taken after injection of the dye were placed in similar small test tubes and compared colorimetrically with the nearest standard. As a strictly quantitative method it is inaccurate, but increased accuracy would in no way enhance its value in the interpretation of liver dysfunction.

*Hemoclastic Test*—The patient was fasted for at least five hours. A leukocyte count was taken. The patient drank one glass of milk and the time was noted. Four consecutive leukocyte counts were taken at half-hour intervals.

## EXPERIMENTAL

*Control Cases*—The six adults selected as controls were patients having medical conditions which had no apparent effect on the hepatic functions. All these cases responded to the tests within normal limits and the results are graphically represented in Chart 1, which shows the average range of variation.

## CONTROL CASES

CASE 1—A man, aged 23. Chronic trachoma. The patient was otherwise healthy.

CASE 2—A man, aged 40. Tuberculosis of the cervical vertebrae. The patient was discharged improved.

CASE 3—A man, aged 28. Tonsillitis, subacute arthritis, heart normal. He was discharged cured.

CASE 4—A man, aged 29 Acute articular rheumatism Complete recovery

CASE 5—A man, aged 29 Gonorrheal ophthalmia The patient was discharged cured

CASE 6—A man, aged 49 Acute empyema Physical signs of right side empyema Thoracotomy and drainage The patient is improving

*Hepatic Congestion*—Passive congestion of the liver from cardiac insufficiency is a common condition Its recognition is of importance from the therapeutic standpoint, but it is a difficult task in those cases where enlargement of the organ is absent Of course not every case of congestion shows impairment and clinically it would be very hard to diagnose The duration of the disease and not the size of the organ is an important factor to consider An acutely congested liver may show practically no impairment unless there is some obstruction to the outflow of bile The hemoclastic reaction was repeated on Case 11 six months later and found to be negative

#### HEPATIC CONGESTION

CASE 7—A man, aged 32 Aortic regurgitation with decompensation Liver slightly enlarged, not tender Not jaundiced The patient improved and was discharged

CASE 8—A man, aged 52 Mitral disease and auricular fibrillation Liver  $2\frac{1}{2}$  inches (6 cm) below costal margin Tender to deep palpation No jaundice The patient was discharged in good condition

CASE 9—A man, aged 43 Myocardial decompensation Liver 4 inches (10 cm) below costal margin Very tender The patient became gradually worse and died soon after the test was performed No necropsy was permitted

CASE 10—A man, aged 37 Mitral disease Gigantism Liver 3 inches (7.6 cm) below the costal margin Painful No jaundice Disease of four years' duration The patient improved and was discharged

CASE 11—A man, aged 61 Chronic myocarditis Passive congestion of the liver Liver 4 inches (10 cm) below the costal margin, pulsating and slightly tender liver The liver was still enlarged and pulsating, but the physical condition was better The patient lived six months after the test was performed

*Neoplastic Cases*—The test was applied to five cases of carcinoma and one of sarcoma Case 12 was selected because metastatic nodules were present at a previous laparotomy The other patients had clinical symptoms, strongly suggestive of metastases of the liver It is important to note the large factor of safety of the organ Only a portion of the normal liver is required to maintain the average physiologic functions of the human body It is evident that the metastatic nodules will produce pressure necrosis on the surrounding liver cells, but unless the nodules are very numerous or very large, there will be enough healthy liver cells left to carry on the normal functions of the organ The same explanation holds good for similar pathologic conditions like abscess or cyst of the liver



## NEOPLASMS

CASE 12—A man, aged 61 Carcinoma of the rectum, of twenty months duration Laparotomy two months before test disclosed metastatic nodules in the liver The organ was not enlarged or tender There was no jaundice The patient was living six months after test

CASE 13—A man, aged 61 Carcinoma of the head of the pancreas Bismuth series negative Liver 2 inches (5 cm) below the costal margin Hard and irregular, not painful The patient was deeply jaundiced and complained of itching The stools were acholic The patient died one month after the test Necropsy showed biliary cirrhosis and the liver completely filled with metastases

CASE 14—A man, aged 60 Carcinoma of the stomach The liver was not enlarged There was no pain or jaundice Bismuth series negative The leukocytic test was done sixteen hours after radiotherapy The patient died three months after the test Necropsy showed some metastases, parenchymatous degeneration and patches of focal necrosis

CASE 15—A man, aged 56 Carcinoma of the rectum Liver  $1\frac{1}{2}$  inches (230 cm) below the costal margin No pain or jaundice The patient died of other causes after being discharged

CASE 16—A man, aged 55 Carcinoma of the colon Diagnosis from bismuth series The liver was negative There was no jaundice The patient died of pneumonia

CASE 17—A man, aged 23 Sarcoma of the right testicle of six months duration The liver could not be palpated, due to a large amount of ascitic fluid Distended abdominal veins and tenderness No jaundice One month after test necropsy showed sarcomatous nodules scattered through the liver

*Cholecystitis*—This group of cases comprised patients in which such diagnosis was primarily made Of the four patients studied, three have completely recovered Cases 19 and 21 show a normal leukocytic reaction, but with evident retention of the dye The curves in these cases rise after the fifteen minute period This sort of retention, also shown in Case 13, gives rise to a typical curve

## CHOLECYSTITIS

CASE 18—A man, aged 60 Cholecystitis? Malignancy? Liver  $1\frac{1}{2}$  inches (230 cm) below the costal margin No pain or jaundice The patient made rapid improvement under treatment

CASE 19—A man, aged 42 Acute angiocholitis Liver 3 inches (76 cm) below the costal margin Very tender Intense jaundice The patient was discharged in good condition after six weeks

CASE 20—A woman, aged 46 Cholangitis or cholecystitis Liver negative, grossly The patient was jaundiced for five weeks Operative drainage of the gallbladder with recovery

CASE 21—A woman, aged 52 Cholecystitis and general paresis The patient was intensely jaundiced The liver was not painful Necropsy three months after the test showed the liver was larger than normal, with passive congestion

*Cirrhosis*—In this disease the fibrosis slowly impairs or destroys the hepatic cells The greater amount of liver tissue destroyed, the greater the dye retention The liver cells take the dye, but are sluggish in getting rid of it Six cases of cirrhosis of the liver showed a uni-

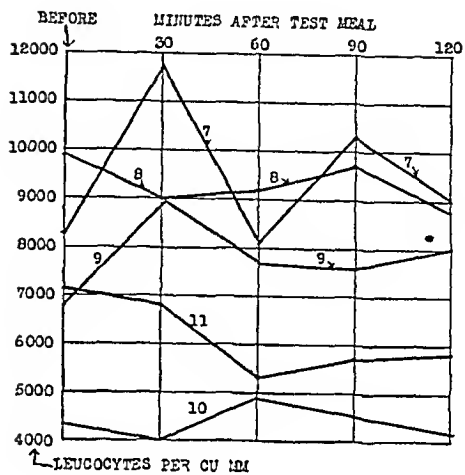
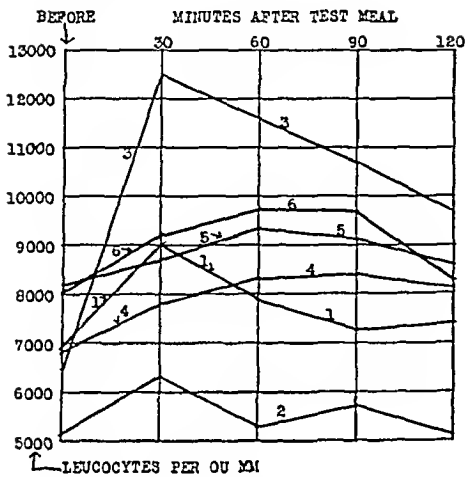
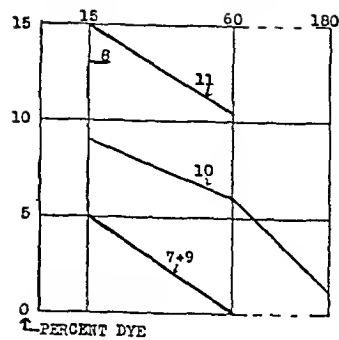
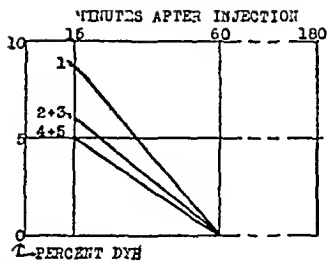


Chart 1—Control cases

Chart 2—Hepatic congestion

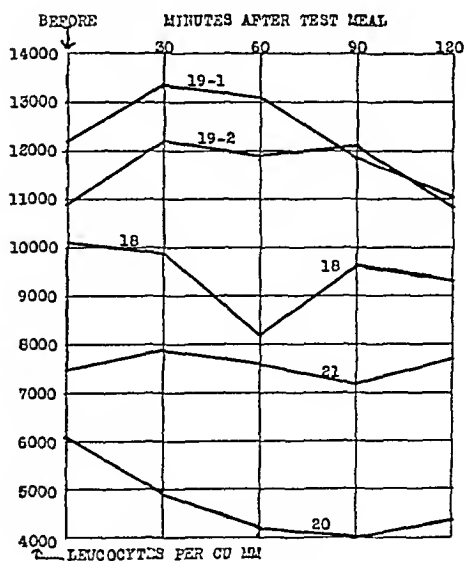
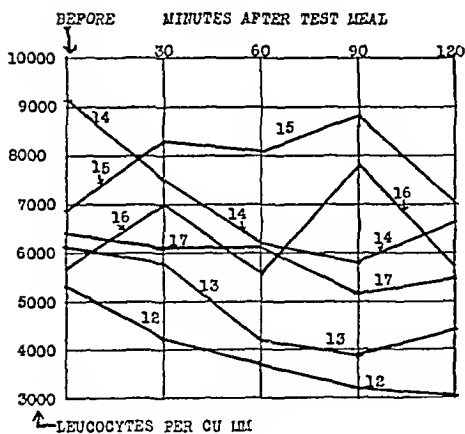
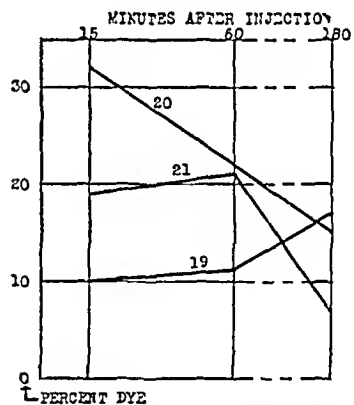
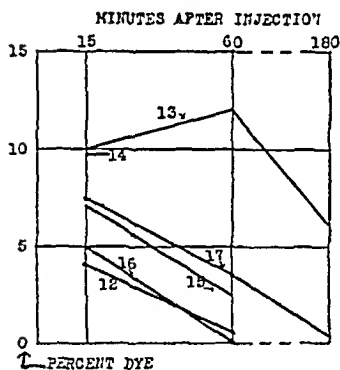


Chart 3—Neoplasms

Chart 4—Cholecystitis

formly moderate retention. The leukocytic test showed a positive curve in all cases. Cases 23, 24 and 27 show a delayed leukocytic reaction. The fact that these cases had ascites suggests a slow absorption of the milk as a cause of the delayed reaction.

### CIRRHOSIS

CASE 22—A man, aged 31. Hypertrophic biliary cirrhosis of about four years' duration. Liver 4 inches (10.16 cm) below the costal margin. Icteric tinge. The patient left the hospital.

CASE 23—A man, aged 56. Atrophic cirrhosis. Ascites. Distended superficial abdominal veins. Hepatic facies. No pain or jaundice. Necropsy one

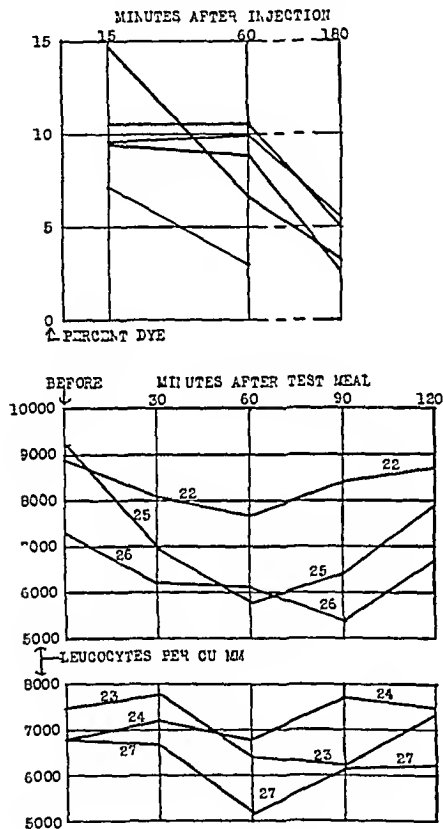


Chart 5—Cirrhosis

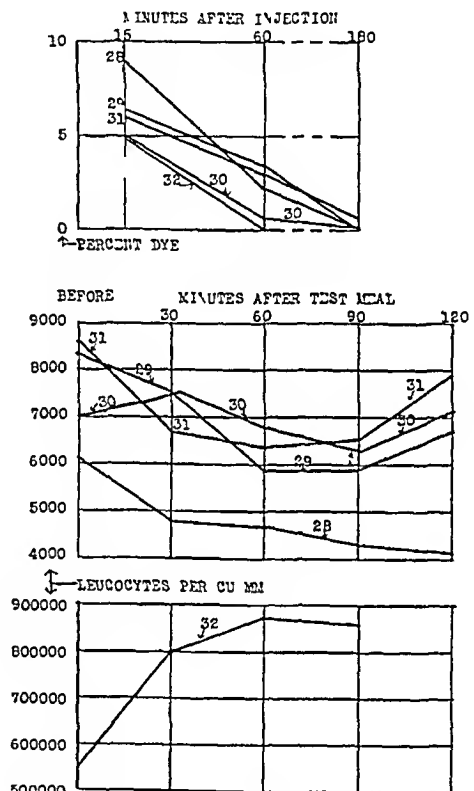


Chart 6—Miscellaneous

month after test showed chronic parenchymatous hepatitis, interlobular cirrhosis.

CASE 24—A man, aged 45. Cirrhosis of liver. Ascites. Enlarged smooth liver. Slight jaundice. No pain. Symptoms suggestive of tabes dorsalis. Necropsy disclosed that the patient died of gastric hemorrhage from varicose veins. Advanced portal cirrhosis. Miliary tuberculosis. The test was done during the hemorrhage.

CASE 25—A man, aged 50. Malignancy. Cirrhosis. Mass in upper abdomen, liver? No pain or jaundice. Wassermann, four plus. Necropsy two weeks after test showed ruptured thoracoabdominal aneurysm. The liver was enlarged, due to the fatty cirrhosis.

CASE 26—A man, aged 35. Cirrhosis with perihepatitis. The liver was 3½ inches (8.33 cm) below the costal margin, and very tender. The spleen was

palpable There was no jaundice Asthenia The history was suggestive of amebic dysentery The patient was discharged

CASE 27—A man, aged 40 Cirrhosis Pulmonary tuberculosis The liver was 3 inches (7.6 cm) below the costal margin, and very tender to pressure Little ascites No jaundice Alcoholic history

*Miscellaneous*—In this group were included two cases of Banti's disease Case 28 was studied before splenectomy, and Case 29 a few days after splenectomy In this connection it is important to note the conclusion of Chaney<sup>6</sup> that cirrhosis of the liver indicates a bad prognosis in splenectomies Although these cases had a positive hemoclastic reaction, there was a small retention of dye, and both operations were followed by good recovery Case 32 is one of lymphatic leukemia The leukocytic counts were done with a red cell counting pipet The results show that the large number of leukocytes did not interfere with the tests In Case 30 the hemoclastic test was repeated six months later and found to give a positive reaction very similar to the first test

#### MISCELLANEOUS

CASE 28—A man, aged 28 Banti's disease The liver was just palpable The spleen large Pronounced anemia No ascites No history of hemorrhage Splenectomy with operative recovery

CASE 29—A youth, aged 13 Banti's disease Very large spleen Liver somewhat enlarged, but no gross appearance of cirrhosis at operation Splenectomy with operative recovery

CASE 30—A man, aged 59 Amyloid disease of the liver Chronic empyema Liver 3 inches (7.6 cm) below the costal margin Not tender Icteric tinge

CASE 31—A man, aged 43 Chronic plumbism Hemiplegia Liver not enlarged No jaundice

CASE 32—A man, aged 38 Lymphatic leukemia Enlarged abdomen and liver hard to palpate No pain or jaundice Necropsy disclosed abdominal lymph glands, greatly enlarged Passive congestion of an otherwise normal liver

#### COMMENT

The liver may be compared to the kidney as an excretory organ The kidney relieves the blood of its water soluble products while the liver removes those which are fat soluble As phenolsulphonephthalein, a water soluble product, is excreted by the kidneys so phenoltetrachlorophthalein, a fat soluble substance, is excreted by the liver Their excretion depends on the same two factors, a normal secreting cell and an open drainage A carcinoma about the ureter or an enlarged prostate will impede kidney drainage in the same manner as angiocholitis will hinder that of the liver There are, however, two distinct differences First, the amount of excretory material passing through the kidney is far in excess of that passing through the liver Second, the

<sup>6</sup> Chaney, W. C. *Am J M Sc* **165** 856 (June) 1923

amount of secreting tissue in the liver is much more abundant than that in the kidney. The conclusion is apparent, that in the same manner as phenolsulphonephthalein gives us information as to kidney function, so should phenoltetrachlorophthalein give us corresponding data on liver function, with the important exception that the liver has a much greater factor of safety. Because of this factor of safety, one can only expect a functional test to detect a more severe dysfunction or one which involves a large number of secretory cells or the patency of the drainage system. Further study of the obscure nature of the hemoclastic test might insure a more delicate interpretation than this latter conclusion would indicate.

Examination of the charts shows a good agreement generally between the hemoclastic and phenoltetrachlorophthalein tests for liver function. There are one or two discrepancies, for which the explanation is not apparent. Some of the results would seem to indicate that the hemoclastic reaction is more sensitive than the dye test (note Cases 28, 29, 30 and 31).

Rosenthal<sup>2</sup> states that in early jaundice due to obstruction, before there is any extensive damage to the cells, dye is removed in practically normal time. The present data do not agree with this statement, but show that there is retention due apparently to the mechanical obstruction, and under these circumstances the hemoclastic reaction is negative (note Case 19 of acute angiocholitis). It is suggested that the leukocytic test measures directly the physiologic integrity of the liver cells, while the dye test measures this integrity dependent on the patency of the biliary drainage system.

As shown by the charts, there may be more dye in the blood stream at the end of one of three hours than there is at the end of fifteen minutes, producing a distinctly typical curve. It is possible that there is a reabsorption of the dye from the bile capillaries by the lymphatics of the liver, in a manner similar to that by which bile itself enters the circulation in cases of jaundice.

The uniformity of the results in cirrhosis is quite striking. The retention is not especially marked and definitely persists at the end of three hours. It emphasizes again the reliability of the liver function tests, when all or a majority of the cells are involved, in contrast to neoplastic metastases where only a portion of the cells are concerned.

The marked leukocytosis in some of the normal cases would cause one to believe that more emphasis should be laid on the relation of diet to the time at which routine leukocyte counts are made in many hospital laboratories.

Localized phlebitis occasionally follows injection of the dye. It is transient and of no consequence. A few patients complained of slight epigastric distress. Catharsis was produced in three cases.

## SUMMARY

1 The hemoclastic and phenoltetrachlorophthalein tests of liver function are used in groups of cases with primary or secondary liver disease. The comparative results of tests are presented, with short comments on each group of cases tested. In many cases the pathologic changes of the organ were determined either at operation or at necropsy.

2 It is suggested that the hemoclastic reaction measures directly the physiologic capacity of liver cells, while the dye test measures this capacity dependent on the patency of the biliary passages.

3 The hemoclastic reaction appears to be more sensitive than the dye test, but a combination of the two is often helpful in diagnosis or even prognosis of obscure hepatic disease.

4 Emphasis is laid on the large factor of safety of the liver, which precludes the use of any functional test to detect minor disturbances of the organ.

# HEMOCHROMATOSIS WITH SPECIAL REFERENCE TO ITS FREQUENCY AND TO ITS OCCUR- RENCE IN WOMEN<sup>1</sup>

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## INTRODUCTION

During one year, from March 1, 1922, to March 1, 1923, ten cases of hemochromatosis came to necropsy in the Pathological Department of the Boston City Hospital, and of these ten, two occurred in women. Another case occurring in a neighboring hospital during this same period was put at our disposal. On going back over the records of the department for the previous twenty-four years, six additional cases were found of which one was a woman.

The rarity of the disease not only clinically but also as a postmortem finding has always been emphasized, and the small number of cases recorded in the literature (less than one hundred) bears this out. Its occurrence in women has frequently been doubted and even denied because only one accepted case has so far appeared in print.

An analysis and discussion of these seventeen new cases, chiefly from the clinical point of view, seems advisable because they present interesting deviations from the textbook picture. In addition, on account of the rarity of female cases their clinical and postmortem records, so far as obtainable, are presented in detail. The literature will be referred to only when necessary.

The clinical observations available are not so complete as could be desired for the following reason. Hemochromatosis can be diagnosed clinically only in its late stages when the clinical syndrome, namely, the signs and symptoms pointing to cirrhosis of the liver, pigmentation of the skin and diabetes are all present. Pathologically, all stages of the disease, from its early beginnings, can be recognized, and on this account a postmortem diagnosis is comparatively simple. In this series of seventeen pathologically advanced cases, all with well marked pigment cirrhosis, only two were recognized during life and proved positive by the demonstration of hemosiderin in an excised bit of skin. Most of the patients died of intercurrent affections, such as lobar pneumonia, meningitis, etc., and a detailed clinical history was often not obtainable. The pathologic diagnosis in all instances was based on the presence of the two pigments characteristic of hemochromatosis, namely, hemofuscin and hemosiderin, in the cirrhotic liver and also in the pancreas and various other organs and tissues.

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\* From the Pathological Laboratory of the Boston City Hospital.

Study of the islands of regeneration<sup>1</sup> in the human cases of pigment cirrhosis shows that the young liver cells are at first nonpigmented, then granules of hemofuscin accumulate in them and in the course of time are transformed into hemosiderin

#### FREQUENCY OF OCCURRENCE

Although occurring quite universally (in China, Japan, Germany, France especially perhaps, England, the United States) hemochromatosis is, as already stated, considered a rare disease. On this account the following statistics from the Pathological Department of the Boston City Hospital, covering a period of twenty-six years, from January 1, 1897 to March 11, 1923, are of interest

Necropsies on adults, 3,760, number of cases of hemochromatosis, 16, percentage of cases of hemochromatosis, 0.42

There are three other well marked cases which cannot be included in this series because they are complicated by the presence of alcoholic hyalin, and it seems best to confine this study to the pure pigment type of lesion

The statistics for the one year, which includes the ten cases, necessarily gives a much higher percentage, a figure which has probably never been reached before

Necropsies of adults, 289, number of cases of hemochromatosis, 10, percentage of cases of hemochromatosis, 3.46

No explanation of this high percentage is evident, for during the succeeding year under exactly the same conditions and with interest unabated, not a single case has been seen. The large number of cases must probably be considered an accidental occurrence

#### CAUSE

Recently<sup>1</sup> it has been shown that it is possible to produce pigment cirrhosis in rabbits by means of chronic poisoning with copper salts, and that the lesion similar to that in hemochromatosis is characterized by the deposition of hemofuscin in the liver and other cells. In the course of time this pigment very slowly changes to hemosiderin

In studying the clinical records of our cases, particular attention has been paid to the possibility of poisoning by copper. The results obtained are strongly suggestive but not convincing. The two most likely sources are an occupation which exposes a person to the inhalation and swallowing of copper dust, and excessive indulgence in distilled liquors

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<sup>1</sup> Mallory, F. B., Parker, Frederic, Jr., and Nye, Robert N. J. M. Res. 42: 461, 1921



The patient (Case 8) from the Peter Bent Brigham Hospital<sup>2</sup> had worked for twelve years in a shop "milling and turning copper and brass" The body presented the typical picture of the disease which was recognized and proved during life Another patient not included in this series, because the lesion was not advanced enough, had worked for six years in a brass foundry and then on account of "brass colic" changed to an iron foundry for the ten years preceding his death While the liver showed but little hemosiderin the stroma around the blood vessels and in the capsule contained relatively large amounts of hemofuscin Evidently the hemofuscin in the liver cells had changed to hemosiderin and had been for the most part gradually removed, but in the connective tissue cells this change had not occurred and therefore the hemofuscin, not being soluble, had persisted

Four other patients in our series had been metal workers and exposed to copper for many years, one spent two years milling and planing brass and then had continued for thirty-six years in the same poorly ventilated, dusty quarters working on high grade steel, another forged metals for twenty-five years in a railroad shop where copper was handled, one was a lineman for a fire department for twenty-three years, fixing cable and telegraph wires, still another worked for thirteen years in a factory polishing pipe wrenches in the same quarters where brass pipes were milled and worked

In six of our cases a history of marked or excessive use of alcohol was obtained In three it was denied, in two no history was available An alcoholic history is of significance because distilled liquors frequently contain copper, often from a trace to 10 mg to the liter, but occasionally in considerable quantity In one sample, analyzed by Dr L T Fairhall,<sup>3</sup> there were 185 mg of copper to the liter The source of the copper in distilled liquors is probably to be found in the action of volatile acids, especially acetic, passing over with the alcohol and acting on the copper coil of the distilling apparatus

Other possible sources of copper are "coppered" peas, beans and pickles, apple butter which is acid and usually cooked in copper kettles, and perhaps copper utensils (kettles, saucepans, hot water heaters, etc) One patient had worked for eighteen years in a cannery cooking fruits in copper kettles In a small proportion of our cases, less than a third, no source of copper poisoning was evident

#### AGE

Hemochromatosis does not occur in children Sprunt<sup>4</sup> states that the disease period is from 30 to 70 years of age but no patient under

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<sup>2</sup> We are indebted to Dr G H Hansmann for the necropsy material and to Dr H A Christian for the clinical history

<sup>3</sup> Personal communication to Dr F B Mallory

<sup>4</sup> Sprunt, T P Hemochromatosis, *Arch Int Med* 8 75 (July) 1911, *Nelson Loose-Leaf Living Medicine* 3 207, 1920

34 was found in the literature. In our series the youngest and incidentally one of the most marked cases was in a woman, aged 31, while the oldest was in a man, aged 84. The advanced age at which the disease makes itself evident clinically is a strong argument in favor of the view that the lesion is exceedingly chronic and requires a minimum of ten years in which to develop. The fact that youth is not affected suggests that it is not exposed to the toxic agent which causes the disease.

#### SEX

Women are usually considered immune to hemochromatosis because, as already stated, only one generally accepted case<sup>5</sup> is on record. The addition of these new cases, all well marked and proved by postmortem examination, must necessarily change this point of view. Evidently the disease is rare in women not on account of any immunity but owing to less exposure to the sources of poisoning which could cause the lesions. We have found the earlier stages of the process in the liver in several other women, sometimes alone, sometimes associated with alcoholic cirrhosis.

#### SIGNS AND SYMPTOMS

The order of occurrence of the lesions of hemochromatosis, which produce the syndrome characteristic of the disease, are cirrhosis of the liver, pigmentation of the skin and sclerosis of the pancreas. Eleven of our series were admitted with signs and symptoms directly referable to one or all of these lesions. The remaining six entered the hospital because of complications (lobar pneumonia, meningitis, etc.). Eight complained of swelling of the abdomen and of symptoms arising therefrom, and five of jaundice. Three had noticed gradual darkening of the skin of the face, neck and arms. A majority when questioned admitted asthenia, loss of weight, and absence of the usual well being. Only one had intermittent dull aching pain in the region of the liver. One was found dead in bed and no cause of death other than the cirrhosis was discovered. One showed the usual train of diabetic symptoms, polyuria, polydipsia and polyphagia. In other words, ten had signs or symptoms pointing to the cirrhosis, three to involvement of the skin and only one to diabetes. The liver was not found to be constantly large. Indeed in most cases it was of small size or within the normal limits. It was not grossly distorted in shape unless complicated by some other condition and the surface was finely nodular, in a number of instances of a "pebble-leather" character, differing from the alcoholic hobnail type. The variations in size of the liver were found to have a very definite relation to the presence of symptoms indicative of obstruction to the flow of blood or bile. When the organ was large

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5 Abbott, Maude E. J. Path. & Bacteriol. 7: 55, 1901.

gastro-intestinal disturbances, abdominal varicosities, ascites and jaundice did not as a rule occur. On the other hand when it was small one or all of these were common. The table shows the weight of the liver and its relation to obstructive symptoms. When its weight was above 1,800 gm (upper normal limit) ascites and jaundice were not present except in two instances as a terminal event. When below this, either persistent jaundice or ascites was almost constant. Of seventeen cases, nine were jaundiced, two, however, only just before death. In two the duration of the icterus exceeded six months. In eight there was ascites and in six the two symptoms were combined. In one there was jaundice, but no ascites owing to well marked compensatory circulation.

The size of the liver probably depends on one or all of several factors, such as the stage of the process, the quantity of toxic agent ingested and the amount of inflammatory reaction to the injury pro-

*The Weight of the Liver and Its Relation to Obstructive Symptoms*

Case	Weight of Liver, Gm	Weight of Spleen, Gm	Evidence of Obstruction in Liver
1	5,400	240	None (primary cancer of liver)
2	3,280		None
3	2,930	405	Jaundice (terminal)
4	2,500	150	None
5	2,215	Small	None
6	2,185	200	None
7	2,015	440	Jaundice (terminal)
8	1,915	180	Ascites (trace)
9	1,900	560	Ascites and jaundice (primary cancer of liver)
10	1,840	230	None
11	1,490	350	Ascites and jaundice
12	1,270	163	Ascites and jaundice
13	1,260	180	Ascites and jaundice
14	1,200	400	Jaundice (well marked compensatory circulation)
15	1,100	290	Ascites
16	1,024	390	Ascites and jaundice
17	Large	250±	Ascites and jaundice (primary cancer of the liver)

duced by it, the presence or absence of regeneration, and rarely fatty infiltration. Probably the time factor is important. In the early stages, necrosis, inflammatory reaction, and regeneration lead to enlargement of the organ. Later, when regeneration plays a less important part and the increased stroma contracts, the organ diminishes in size. If the process is very slow, the circulation of the blood and the flow of the bile may accommodate themselves to the condition so that obstruction of either does not occur. If, however, the changes are more rapid, blocking of the blood and bile may result and ascites and jaundice take place. As a result of the liver lesion death may occur before the other signs of the syndrome have had time to develop.

The size of the spleen (see table) bears no relation to the size of the liver. It was by no means constantly large, for in five cases it was below 200 gm. These particular findings as regards the liver and spleen are of special interest because they vary widely from what has been described. Thus Sprunt,<sup>4</sup> in summing up the literature, says in part

"The liver is characteristically large and irregular, and may be tender. The spleen is also enlarged and as a rule is easily palpable. There is no jaundice."

Pigmentation of the skin, the second of the classical signs, usually precedes the diabetes and is of two distinct types.<sup>1</sup> The characteristic type is due to the presence of the hematogenous pigments, hemofuscin and hemosiderin in the corium, especially around the coil glands, but also in the subcutaneous fat tissue. It shows itself as a dull gray-brown or dirty brown discoloration of the skin of the extremities (face, neck, forearms, hands, front of wrists, legs). A positive diagnosis of hemochromatosis during life is based on the demonstration of the presence of hemosiderin in an excised piece of skin.

The other type of pigmentation is due to increase of melanin in the skin and other organs and tissues of the body in places where it normally occurs, and is without much question due to injury of the adrenal glands by the accumulation of the hemotogenous pigments there. In other words, Addison's disease is produced. As the lesion in the adrenals is confined practically to the zone glomerulosa it would seem as though destruction of this layer was chiefly responsible for the increase of the melanin.

The two types of pigmentation ordinarily occur separately but may and do occur together, and this probably accounts for the variations in the descriptions of the appearance of the skin in hemochromatosis by different authors.

Diabetes mellitus is always a late symptom when due to the pigmentation, necrosis and sclerosis of the pancreas, but hemochromatosis may of course complicate diabetes that is already existing. One of the two cases in our series had been a mild diabetic patient for years. In the other, diabetes followed pigmentation of the skin and ran a rapid and progressive course to a fatal termination.

Complications of the disease are of frequent occurrence, as with any other very chronic disorder but it has one sequela, primary liver cell carcinoma, which is relatively frequent and which it shares with the other chronic lesion of the liver, namely, alcoholic cirrhosis. In our series of seventeen cases we had three well marked examples. The lesion evidently arises as a result of the continued necrosis and regeneration of liver cells. Some one cell eventually gets beyond normal control and proceeds to proliferate with the resulting formation of a carcinoma. Whenever the liver is unusually large, and particularly when the increase in size is not uniform, superimposed malignancy should be suspected. In Case 1 the right lobe was found to be almost entirely replaced by tumor, and the hepatic vein and inferior vena cava almost completely occluded by a cancerous thrombus without, however, at any time causing obstruction to the flow of blood or bile.

## HEMOCHROMATOSIS IN WOMEN

Besides the one generally accepted case<sup>5</sup> two others have been claimed but never proved. This one case had a strong alcoholic history.

In our series the first patient of the three cases occurring in women also had an alcoholic history. Little else is known because she was found dead in bed. Necropsy showed a large liver and intense generalized pigmentation, with a slight amount of iron pigment in the skin but no ascites or jaundice. The other two cases gave no history of alcoholism, both were jaundiced and one had ascites. The livers were small.

## REPORT OF CASES

CASE 1—C. H., a woman, aged 31, was found dead in bed, July 30, 1902. A long history of alcoholism was obtained.

The necropsy showed a well developed, fairly well nourished, white woman. No marks of violence were present. Pigmentation of the skin was not obvious. The myocardium was a dark reddish brown, otherwise the heart was negative. The lungs and spleen were grossly negative. The pancreas was a dark chocolate brown color. The liver weighed 2,500 gm. Its surface was dark brown and finely nodular. The consistency was definitely increased. On section, the cut surface was brown with fine interlacing slightly depressed darker chocolate brown strands of tissue which divided it off into islands, varying up to 3 mm in diameter. The kidneys were not grossly remarkable. The adrenals showed a dark brown line just beneath the capsule. The endometrium was characterized by a similar but fainter brown tint. In gross, the Prussian blue reaction was intense in the liver, heart, pancreas, cortex of adrenal, stomach, duodenum, and less marked in the kidneys, ovaries, spleen and cervical mucous membrane.

Microscopically, the heart muscle, pancreas, liver, kidney, mucosa of stomach and duodenum, and retroperitoneal lymph nodes showed hemosiderin and hemofuscin in characteristic locations. The liver showed an increase in the periportal connective tissue, which was diffusely infiltrated by endothelial leukocytes engorged with hemosiderin. In many places, especially about vessels, the fibroblasts themselves contained hemofuscin and hemosiderin. The liver cells throughout were loaded with hemosiderin. Here and there small islands of these showed only small amounts of hemosiderin and hemofuscin. No alcoholic hyalin was present. Traces of hemosiderin were present about the coil glands of the skin.

CASE 2—N. K., a woman, aged 65, was admitted to hospital, Nov. 16, 1922, and died nine days later. Her complaints were swelling of the abdomen and jaundice.

*Past History*—The patient's habits were good. No alcohol. She lived an easy life with her daughter, and was always healthy with one exception until onset of present illness, five years ago she had an attack of jaundice which cleared up without treatment in six weeks.

*Present Illness*—Began seven weeks before death with insidious onset of jaundice. The abdomen also began to swell and a physician was called. Fluid was drawn off but soon recurred. Jaundice persisted and the abdomen was tapped many times before admission. During this time patient was not ill enough to be confined to bed.

*Present Examination*—An emaciated white woman was seen moaning in bed. The sclerae were slightly jaundiced. The heart and lungs were normal. The abdomen was distended by fluid and gas. There was shifting dullness in the flanks, and slight edema of the ankles. Otherwise there was nothing worthy of note.

November 22, the abdomen was tapped. From 10 to 11 liters of straw colored fluid was withdrawn. The edge of the liver was felt. The patient died some hours later.

Necropsy revealed a poorly developed and poorly nourished white woman. The sclerae were jaundiced. Edema of the legs was present. The skin was yellow-gray with brown spots resembling freckles on the arms and legs. There was a fluid wave in the abdomen. In the peritoneal cavity was 1,500 c c of dark, amber colored fluid. There were adhesions in the region of the gallbladder. The mesenteric and retroperitoneal lymph nodes were enlarged and dark colored. Prussian blue reaction was marked. The pleural and pericardial cavities were normal. The heart, lungs, spleen, kidney and adrenals were essentially negative. The liver weighed 1,260 gm. Its surface was grayish-brown, finely nodular, hard, tough and leathery. The cut surface was deep brown with fine brownish-green slightly depressed strands traversing it. Aorta showed generalized sclerosis with calcification. Prussian blue reaction was marked in the liver, lymph nodes and spleen.

Microscopically, the liver showed moderate increase in periportal fibrous tissue. Many of the fibroblasts were loaded with hemofuscin, especially about the arteries. This fibrous tissue was infiltrated by endothelial leukocytes engorged with hemosiderin. The liver cells were filled with hemosiderin. The islands of regeneration showed both pigments. The retroperitoneal lymph nodes and spleen were infiltrated by endothelial leukocytes engorged with hemosiderin. Fibroblasts of the stroma contained both pigments in moderate amounts.

CASE 3—E D B, a woman, aged 60, who showed at necropsy marked dilatation of the veins of the abdominal wall and of the esophageal plexus, a small (1,200 gm) nodular cirrhotic liver, a large spleen and jaundice. Microscopically, no alcoholic hyalin could be found in the liver. Hemosiderin and hemofuscin were present in liver and pancreas, in characteristic distribution. The spleen was negative but convoluted tubules of the kidney showed much hemosiderin.

#### SUMMARY

This paper presents an analysis of seventeen cases of hemochromatosis, which with one exception came to necropsy at the Boston City Hospital during the last twenty-six years. Fourteen cases were patients in the wards, and ten, or 62 per cent came to necropsy during one year (1922-1923).

The series includes three women.

Five patients in their occupations had had long exposure to copper, and at least six cases had a strong alcoholic history.

Six patients were admitted with symptoms directly referable to the disease. Eight complained of swelling of the abdomen or symptoms therefrom, and five of jaundice. Three had noticed gradual darkening of the skin of the face, neck and arms. One patient was found dead in bed, and no cause of death other than the hemochromatosis was discovered. Six patients were admitted, and died because of associated but irrelevant lesions. Three died of superimposed primary liver cell carcinoma.

The spleen varied in size from large to small, and the variations were not related to the size of the liver.

Skin pigmentation is of two types, one due to hematogenous pigments the other to melanin.

Hemochromatosis may be complicated by alcoholic cirrhosis and vice versa

#### CONCLUSIONS

Chronic poisoning with copper may be the cause of hemochromatosis. The most likely sources of the copper are occupations involving exposure to copper and brass, excessive indulgence in distilled liquors, and possibly "coppered" food stuffs.

The liver is not constantly large, it may be small but is often of normal size.

The spleen may be large or small.

Ascites and jaundice both occur. Their frequency bears a definite relation to the size of the liver.

The disease occurs in females.

Primary liver cell carcinoma is a not infrequent sequela.

# A CLINICAL STUDY OF BLOOD FIBRIN

WITH OBSERVATIONS IN NORMAL PERSONS, PREGNANT WOMEN,  
AND IN PNEUMONIA AND LIVER DISEASE \*

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## INTRODUCTION

Foster and Whipple<sup>1</sup> have reported a method for the quantitative analysis of blood fibrin which is suitable for clinical investigation because it is relatively accurate, and requires but 5 c c of blood on analysis. Their work demonstrated that small variations in the level of blood fibrin occur in normal dogs while disease (experimentally produced) in these animals causes very wide and rapid fluctuations of this blood protein.

Injury to any tissue, excepting the liver, was found to cause an increase in the blood fibrin content. This increase was constantly observed, for example, when sterile abscesses were produced by the subcutaneous injection of turpentine, when the animal was exposed to massive doses of deep roentgen rays or when suffering from "distemper," a common acute respiratory infection in dogs. If the liver is severely injured, as by chloroform or phosphorus, a decrease and not an increase in blood fibrin occurs. However, following mild as opposed to severe liver injury, there tends to be a rise instead of a fall. These observations on animals led to the clinical investigation reported in the present communication.

Older methods of fibrin and fibrinogen analysis have been discussed and compared with the method used here, in the work by Foster and Whipple<sup>1</sup>. Cullen and Van Slyke<sup>2</sup> in 1920 and Gram<sup>3</sup> in 1921 have reported methods of analysis which give results similar to those obtained in the present work.

## NORMAL FIBRIN VALUES

The most extensive series of fibrin determinations in health and disease yet published is that by Gram<sup>4</sup>. His figures for the normal

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\* From the Medical Laboratories of the Massachusetts General Hospital.

\* This paper is No. 35 of a series of papers on the physiology and pathology of the blood, from the Harvard Medical School and allied hospitals, a part of the expense of which has been defrayed by a grant from the Proctor Fund for the study of chronic disease.

1 Foster, D. P., and Whipple, G. H. *Am J Physiol* **58** 365 (Jan.) 1922.

2 Cullen, G. E., and Van Slyke, D. D. *J Biol Chem* **41** 587 (April) 1920.

3 Gram, H. C. *J Biol Chem* **49** 279 (Dec.) 1921.

4 Gram, H. C. *Acta Med Scandinav* **56** 107 (March) 1922 (article in English).



fibrin are based on twenty-five analyses on men and the same number on women. His average results and those of other investigators are compared with mine in Table 1. The average figures presented in this paper are based on duplicate analyses on twenty-three normal men and nineteen normal women.

The results reported by Hammarsten<sup>5</sup> and Mathews<sup>6</sup> are based on a small number of analyses and were computed before the more accurate methods were devised. Their figures are, therefore, probably less accurate than those of later workers. Whipple's<sup>7</sup> figures are styled by him as "normal or approximately normal." He has included cases which show results we now know to be abnormal.

TABLE 1—*Fibrin Determinations in Normal Persons Taken from the Literature*

Investigator		Men		Women		Men and Women, Fibrin per 100 C c Plasma
		Fibrin per 100 C c Plasma	Fibrin per 100 C c Blood	Fibrin per 100 C c Plasma	Fibrin per 100 C c Blood	
Hammarsten	Maximum					650
	Minimum					101
	Average					420
Mathews	Maximum					600
	Minimum					150
	Average					375
Whipple, 7 determinations	Maximum					591
	Minimum					385
	Average					505
Foster and Whipple, 4 determinations	Maximum	364	178			
	Minimum	316	163			
	Average	335	172			
Gram 50 determinations	Maximum	360	190	380	210	
	Minimum	200	110	210	120	
	Average	270	140	290	170	
Foster, 42 determinations	Maximum	446	210	470	233	
	Minimum	256	112	255	143	
	Average	332	163	344	179	

Table 2 gives in detail the results of the fibrin analyses, from which the average figures recorded in Table 1 for the present work were computed.

The data in Table 3 is presented primarily to emphasize the fact that the extremes of normal fibrin values recorded are rarely reached, the vast majority of results falling within the limits for men of from 250 to 400 mg per hundred cubic centimeters of plasma or from 125 to 200 mg per hundred cubic centimeters of blood. The extreme values reported by Mathews,<sup>6</sup> Hammarsten<sup>5</sup> and Whipple<sup>7</sup> were not observed.

5 Hammarsten, Olof. *A Text Book of Physiological Chemistry*, New York, John Wiley & Sons, 1914.

6 Mathews, A. P. *Physiological Chemistry*, New York, William Wood & Co., 1920.

7 Whipple, George H. *Am J Physiol* 33 50, 1914.

The figures for women show a similar variation, but are slightly higher, being from 300 to 425 mg per hundred cubic centimeters of plasma or from 150 to 225 mg per hundred cubic centimeters of blood. It seems

TABLE 2—*Normal Fibrin Values*

Men								Women							
Fibrin								Fibrin							
Age	Tem- pera- ture, F	Pulse Rate per Min	Hema- toerit, per Cent Red Blood Cells	Aver- age Two Deter- mina- tions, Mg	100 O c Plasma, Mg	100 O c Blood, Mg		Age	Tem- pera- ture, F	Pulse Rate per Min	Hema- toerit, per Cent Red Blood Cells	Aver- age, Two Deter- mina- tions, Mg	100 O c Plasma, Mg	100 O c Blood, Mg	
22	98	66	48	4.65	296	153		22			56	5.45	353	155	
30	97.6	80	54.5	7.3	405	184		24			47	5.0	304	161	
28	97.6	72	54.0	6.15	390	178		43			48	6.0	373	194	
25	97.6	64	38	5.65	287	178		52			44	6.15	374	210	
39	99	78	54	5.7	354	165		35	98.6	78	44.5	5.05	306	167	
45	98.2	72	56	4.05	256	112		21	98.6	80	44	4.2	255	143	
49	98	60	51	4.2	264	129		25	98	78	46.5	5.3	320	171	
27	98.6	70	57	5.25	342	147		21	98.6	82	46	5.2	321	173	
61	98	80	50	4.85	287	143		21	98	76	44	5.4	323	181	
57			53	7.0	446	210		26*			42	5.0	293	173	
63			49	6.0	372	190		16			48	5.45	342	178	
48			49.5	6.35	390	196		24			44	5.2	314	176	
22			54.5	5.4	340	155		45	98.6	78	51	7.3	475	232	
11			43.5	6.1	370	193		58	98	82	46.5	6.2	378	202	
23			54.5	5.0	320	145		23	98.6	80	45.0	6.1	371	204	
24			49	5.0	322	164		33	98.6	90	47.5	5.5	342	180	
27	98	72	49.5	5.0	310	156		53	99	90	43.5	6.3	382	216	
40		82	51	6.05	382	187		63	98.6	88	47.6	6.55	400	209	
3	98.2	82	51	4.9	305	150		27	99	88	50.6	6.65	411	203	
23	99	80	52	4.65	292	139									
50			52.5	6.1	339	161									
28	98	70	51.6	6.3	388	187									
55			44.6	4.85	305	169									
Averages			49		332	163					46		344	179	
Highest			57		446	210					56		475	233	
Lowest			38		256	112					42		255	143	
Difference be- tween highest and lowest			15		190	98					14		220	90	

TABLE 3—*Distribution of Fibrin Values in Normal Men and Women*

Men				Women			
Fibrin per 100 O c Plasma, Mg	Number of Cases	Fibrin per 100 O c Blood, Mg	Number of Cases	Fibrin per 100 O c Plasma, Mg	Number of Cases	Fibrin per 100 O c Blood, Mg	Number of Cases
450 and above	0	225 and above	0	475 and above	1	250 and above	0
425 to 449	1	200 to 224	1	450 to 474	0	225 to 249	1
400 to 424	1	175 to 199	9	425 to 449	1	200 to 224	8
375 to 399	4	150 to 175	7	400 to 424	3	175 to 199	5
350 to 374	3	125 to 149	5	375 to 399	2	150 to 174	6
325 to 349	3	100 to 124	1	350 to 374	4	125 to 149	1
275 to 299	4			300 to 324	6		
250 to 274	2			275 to 299	1		
				250 to 274	1		
300 to 324	5			325 to 349	2	100 to 124	0

possible that the extreme values recorded may be due to some clinically unrecognized pathologic conditions. That there is a normal variation in fibrin values seems to be established by Gram's work and by that of Foster and Whipple on dogs as well as by the data offered here.

## FIBRIN VALUES IN NORMAL PREGNANCY

Before undertaking the study of fibrin in the toxemias of pregnancy, ten estimations were made on normal pregnant women to ascertain the physiologic variation in this state. Gram<sup>4</sup> found that as pregnancy progresses, the blood fibrin level rises. This observation was confirmed by the present work. The patients examined were in from the sixth to the eighth months of pregnancy and were clinically free from disease. Table 4, in which the results of these determinations are given, shows the average fibrin value for the plasma to be 415 mg per hundred cubic centimeters in pregnant women as compared with 344 mg per hundred cubic centimeters in the nonpregnant. The average value for the whole blood was found to be approximately 94 mg higher in pregnancy.

TABLE 4—*Fibrin Values in Normal Pregnant Women*\*

Month of Pregnancy	Systolic Blood Pressure	Hematocrit, per Cent Red Blood Cells	Fibrin			Remarks
			Average Two Determinations, Mg	100 Cc Plasma, Mg	100 Cc Blood, Mg	
6	125	37	5.8	346	218	Slight edema of legs Constant leukorrhea
8	120	43	9.0	540	308	
8	120	37	6.6	391	246	
8	100	46	7.6	473	255	
8	105	39	7.2	430	262	Slight trace of albumin in urine
8	130	38	8.0	475	295	
7	110	38	6.6	402	250	
8	110	42	8.4	505	294	
8	115	38	9.8	532	330	
9	110	39.6	7.6	455	275	
Averages		38.9		414.9	273.3	
Highest		46.0		540	330	
Lowest		37.0		346	218	
Difference between highest and lowest		9.0		194	112	

\* The temperature of these women was normal.

## FIBRIN VALUES IN TOXEMIA OF PREGNANCY

In view of the foregoing experiments on dogs with liver necrosis<sup>1</sup> it was anticipated that patients suffering from toxemia of pregnancy might show a pathologic fibrin curve, because these patients at necropsy typically show some degree of liver necrosis. It was found that toxemia suspects fell into two groups: (1) patients with nephritis and (2) patients without nephritis. Blood pressure readings and the albumin examinations of the urine are included in the tables, as they are the most reliable clinical data suggesting the onset of toxemia. Whether a patient had chronic nephritis or not was finally determined by examination several months postpartum for clinical and laboratory evidence of this disease. In this series of six cases, with symptoms suggesting toxemia (headache, lassitude, loss of appetite, elevated blood pressure,

together with edema and albuminuria), those demonstrated to have nephritis showed a normal or but slightly elevated blood fibrin, while the cases of eclampsia and preeclamptic toxemia tended to show a more marked elevation of the blood fibrin level. In neither group did the fibrin values become subnormal, and none of the cases studied were fatal. Only one of the typical cases of toxemia had convulsions, and

TABLE 5—*Fibrin Values in Four Cases of Toxemia of Pregnancy*

Date	Blood Pressure		Hemato- crit Red Blood Cells, per Cent	Fibrin			Remarks
	Sys- tolic	Dias- tolic		Average Two Determi- nations, Mg	100 Cc Plasma, Mg	100 Cc Blood, Mg	
Mrs H	Mild toxemic symptoms			No convulsions			
7/ 1	140	100	39.0	8.0	486	297	Urine, very slight trace albumin
7/ 2	140	100	39.5	8.4	492	298	Symptomless
7/ 3	150	100	39.5	8.0	475	286	
7/ 5	159	112	44.5	8.6	510	280	Edema of hands, urine, slight trace albumin, headache
7/ 7	160	120	41.8	7.3	440	256	
7/ 8							Delivered (low forceps)
7/11	130	100	39.0	10.1	580	354	
7/15	130	90	38.0	8.2	485	292	Normal convalescence, urine, very slight trace albumin
Mrs B	Moderately severe toxemia			No convulsions			
6/23	180	?	90				Bled, 250 cc
6/29	130	80	33	10.2	596	400	Urine, slightest possible trace albumin, clinically toxic
7/ 1	140	90	32.6	9.9	576	389	
7/ 3	140	90	27.0	8.2	470	344	Clinically improved
7/ 4							Discharged, home
7/ 7	120	80	26.4	8.4	478	351	Nonprotein nitrogen (blood), 34.8 mg per 100 cc
7/ 8	130	90	28.0	7.9	450	324	
7/26							Delivered of twins
7/29	130	90	29	9.4	590	416	This rise is probably due to the repair of uterine trauma of birth, and is normal and regularly seen
Mrs Mc	Severe toxemia			No convulsions			
7/13	140	100	44	10.4	632	355	Slight trace albumin in urine
7/17	150	100	48	9.3	570	296	
7/19	130	100	47	8.6	650	286	
7/21	140	100	45	10.0	622	342	Edema of shins and eyelids, headache, malaise
7/23							Delivered
7/27	135	100	33	9.3	555	380	
8/ 2							Blood nonprotein nitrogen 38.4 mg per 100 cc, urine, slightest possible trace albumin, report from Mass Gen Hosp "no evidence of chronic nephritis"
Mrs D	Very severe toxemia			Convulsions			
7/11	170	150	51	10.8	670	329	Slight tinge of bile in plasma, slight trace urinary albumin
7/13	220	170					Bled, 420 cc
	160	140	46	9.4	612	330	Had a convulsion after the delivery of dead fetus
7/15	120	100	39	9.0	550	336	Still dangerously ill
7/17	125	90	43	12.8	760	435	Rise here probably due to birth trauma and infection, temperature 101
7/21	110	85	45	8.5	508	280	Clinically much improved, renal function, 40 per cent

the highest fibrin values are recorded for this case. The severity of the symptoms and the degree of fibrin elevation run parallel in this small series of observations.

Table 5 gives fibrin values obtained on succeeding days in four cases of true toxemia of pregnancy of varying grades of severity. Table 6 gives interval readings in two cases of nephritis during pregnancy.

The difference in the figures obtained in nephritis and those found in patients with true toxemia of pregnancy indicates that the underlying pathologic physiology in these two conditions is in all probability dissimilar

The most severe case of eclampsia studied gave a high rather than a low blood fibrin value, contrary to what might be expected in severe liver injury. This fact would indicate that the symptoms in these patients are probably not due to liver insufficiency. This opinion is supported by the observation that the two patients with acute liver atrophy, while showing typical symptoms of liver insufficiency, did not have convulsions. It is noteworthy in this connection that none of the animals in Foster and Whipple's experiments with livers injured by

TABLE 6—*Fibrin Values in Two Cases of Pregnancy with Nephritis*

Date	Blood Pressure		Hemato- crit Red Blood Cells, per Cent	Fibrin			Remarks
	Sys tole	Diastole		Average Two Determinations, Mg	100 Cc Plasma, Mg	100 Cc Blood, Mg	
Mrs C R	Clinically very ill						
7/ 3	160	100	34.6	6.8	396	256	Urine, slight trace albumin and rare casts
7/ 5	170	110	40.5	7.8	460	248	Phthalein test, 40 per cent 1/25, blood urea "normal"
7/ 5							Delivered by cesarean
7/13	130	100	34.0	10.1	635	420	Wound septic
1/25	120	90					Urine, slight trace albumin and casts
Mrs C an	Clinically very ill						
7/ 2	175	110	41.5	6.8	405	242	Urine, slightest possible trace albumin, edema
7/ 3	175	110	41.5	5.6	334	199	
7/ 5	190	110	47.0	8.6	515	278	
7/ 7	175	110	44.4	7.4	445	249	
7/ 8							Delivered
7/ 9	140	100	43.0	8.0	480	274	
7/11	150	94	44.5	7.75	475	264	Blood nonprotein nitrogen, 39.3 mg per 100 Cc
7/13	170	120	42.0	7.7	455	262	
7/15	160	110	43.0	6.2	368	210	
7/17	170	110	42.0	6.6	394	228	
2/20	184	96					Urine, slightest possible trace albumin

chloroform anesthesia or phosphorus died when the fibrin content of the blood remained above normal. It was only when the liver injury was severe enough to cause a low blood fibrin that death occurred.

The postpartum fibrin rise, recorded in Tables 5 and 6, is probably best explained as being due to the trauma incident to birth, for injury to any tissue excepting the liver causes an increase in the fibrin. If infection is present, this postpartum rise is still more marked (see Mrs. D, Table 5).

The patients with nephritis were equally as sick, judging from clinical evidence, as the case of "severe toxemia" (Mrs. Mc, Table 5). But it will be noted that the fibrin value in the latter was 622 mg per hundred cubic centimeters of plasma or 342 mg per hundred

cubic centimeters of whole blood, while the highest value in the former was 515 mg per hundred cubic centimeters of plasma or 278 mg per hundred cubic centimeters of whole blood. An estimation of the blood fibrin should, therefore, aid in the differential diagnosis of toxemia of pregnancy and nephritis accompanying pregnancy. Inspection of Gram's<sup>4</sup> determinations reveals evidence to support such a possibility. He reports two cases of nephritis complicating pregnancy, with plasma fibrin values of 580 and 480 mg per hundred cubic centimeters or a whole blood fibrin figure of 290 mg per hundred cubic centimeters in both cases. His one case of toxemia of pregnancy had a plasma fibrin of 700 or a whole blood fibrin of 390 mg per hundred cubic centimeters.

#### FIBRIN VALUES IN LIVER ATROPHY

Two cases of liver atrophy, with subsequent necropsy, showed subnormal fibrin levels in both plasma and whole blood. In one patient very vigorous treatment with arsphenamin was the probable cause of atrophy, while in the other patient the etiology was not known. Table 7 gives the results in Case 1.

TABLE 7—*Fibrin Values in a Case of Acute Liver Atrophy*

Date	Temperature, F	White Blood Count, per Cu Mm	Fibrin	
			Per 100 C c Plasma	Per 100 C c Blood
November 27	98.6		208	90
November 28	99.0		250	125
November 29	99.4	8,800	135	67
December 1	100.0	7,300	280	140
December 4	102.5	13,700	356	188

CASE 1—R, a man, admitted to Massachusetts General Hospital, had had arsphenamin treatment. Because infection influences the fibrin curve, the temperature and white blood cell counts are included in the table. It will be noted that with the onset of a terminal infection, as indicated by the rising temperature and white count, the fibrin level rose. A similar reaction was observed by Foster and Whipple<sup>1</sup> in dogs with experimental liver injury, when sterile abscesses were produced by the subcutaneous injection of turpentine.

*Necropsy*—Liver. The organ weighed 900 gm (normal from 1,300 to 1,400 gm). The surface in places was granular and the edges thin and sharp. On section there was some increase in consistency. The sectioned surfaces did not show definite evidence of softening. Vessels were engorged. Gallbladder and ducts were normal. Microscopic sections of the liver showed central degeneration over wide areas, in a few sections, restricted areas of cirrhosis and many bile ducts. Lungs. The pleura showed a thick fibrino-purulent exudate adhering to the surface. On section, the lung was moist but no pneumonia areas were seen or felt.

CASE 2—Mrs. D, an Italian housewife, aged 48, was admitted to Massachusetts General Hospital, with a history of liver atrophy. By our method of analysis only a few shreds of fibrin were recovered. So small was the amount of fibrin present that quantitative estimation was impossible although determinations were attempted on three consecutive days.

*Necropsy*—The liver weighed 700 gm. The capsule generally was rather smooth except toward the margins where there was some fine wrinkling. Showing through the capsule here and there were small, discrete, brownish-red areas. Elsewhere the surface showed a dull, reddish color. On section, these brownish-yellow areas were found to be slightly softer than the surrounding, more nearly normal appearing tissue. The gallbladder and ducts were negative. The bile was thick and stringy.

Microscopic examination showed the absence of hepatic cells over wide areas. The tissue in such areas consisted almost entirely of a hemorrhagic stroma in which were groups of structures like bile ducts. In places islands of liver cells were present. One or more of the sections showed liver tissue in which were areas devoid of liver cells and infiltrated with mononuclear cells. Examination of kidney, spleen and pancreas was negative.

#### FIBRIN VALUES IN POSTARSPHENAMIN JAUNDICE

Five cases of postarsphenamin jaundice were studied. None of these cases were deeply jaundiced and none were fatal. During 1920 and 1921 twenty cases of jaundice from arsphenamin were observed in this hospital. The typical symptoms in these cases were malaise and anorexia, followed in two or three days by jaundice. Some patients noticed had light colored stools and dark colored urine, a few had infrequent attacks of vomiting. The time that elapsed after the last arsphenamin injection and the development of jaundice varied from one to ninety-one days. Jaundice in the nonfatal cases persisted from twenty to sixty days. The course of the disease, after entrance to the hospital, in the fatal cases was from four to twelve days. From five to twelve intravenous treatments of 0.4 gm. of arsphenamin or 0.6 gm. of neoarsphenamin had been administered.

The fibrin values in the nonfatal cases studied were all above normal, indicating that the liver damage was not very severe. Table 8 gives the fibrin values for five of the cases studied. The findings in other cases were similar.

In considering these data it will be recalled that the gallbladder and bile ducts were normal in Mr. R. Further, Gram<sup>4</sup> reports (Table 52) four cases of catarrhal jaundice with an average plasma fibrin of 380 mg. per hundred cubic centimeters and an average blood fibrin of 210 mg. per hundred cubic centimeters. One case of catarrhal jaundice studied by the author had a plasma fibrin of 387 mg. per hundred cubic centimeters, or a blood fibrin of 176 mg. per hundred cubic centimeters. Five duplicate determinations were made on this case during one week, from which this average was computed. These results seem to indicate that postarsphenamin jaundice is due to parenchymal liver injury and not to pathologic changes in the bile ducts.

#### FIBRIN VALUES IN LOBAR PNEUMONIA

It has long been known that pneumonia is associated with high blood fibrin. Foster and Whipple<sup>1</sup> (Paper 4, Table 53) give the results

TABLE 8—Fibrin Values in Five Post Arsphepnam Jaundice Cases

Date	Age	Stage of Syphilis	Arsphen- amin Gm	Mercury Received, Grains	Phthaloin Renal Function, per Cent	Stool Color	Tempera- ture, F	Urinary Albumin	Hemato- crit Red Blood Cells, per Cent	Fibrin			Remarks
										Average Two Deter- minations, Mg	Per 100 C c Plasma, Mg	Per 100 C c Blood, Mg	
Case 1 2/11/21	60	Late tertiary	1.8	6	60	Gray	99	Very slight trace	42.5	10.35	624	358	Liver not palpable
2/12/21							98		41.0	9.8	585	326	
2/11/21							97.8		11.5	7.3	138	213	
2/15/21							97.4		15.5	5.0	340	185	
Case 2 1/29/21	53	Late tertiary	1.2	6	45	Light brown	99	None	50.0	6.75	115	207	Liver dullness at sixth rib, edge felt 2 cm below costal margin
1/30/21							100		49.0	7.3	486	248	
2/ 1/21							98.8		51.0	6.5	410	200	Coagulation time 9 minutes
2/ 2/21							98.6		48.0	7.0	428	222	Stool guaiac test negative
2/ 3/21							99		51.0	7.15	111	217	
Case 3 7/ 9/20	92	Late secondary	1.8	15		Brown	98.6	None	53.0	5.9	370	174	Most severe case, very toxic, liver dullness at fifth rib, edge not felt
7/11/20							99		50.0	7.7	490	215	Clinically better
7/13/20							99		50.0	8.2	510	255	Almost free from jaundice
Case 4 6/10/20	25	Late secondary	1.2	5	35	Light brown	98.6	Slight trace	46.0	6.1	400	213	Liver dullness from fifth rib to costal border
6/12/20							98		47.0	6.8	115	220	
6/16/20							99		47.5	7.2	115	231	
6/21/20							98.8		45.0	7.2	111	211	
Case 5 6/16/20	53	Tuberc- ulous				Light yellow Light brown	99	Very slight trace	45.5	6.45	400	218	Liver edge felt 7 cm below eos- tal border
6/21/20							98.6		49.5	6.9	420	208	
6/23/20							98		49.0	7.6	400	236	
6/26/20							97		50.5	7.5	461	230	



obtained in nine cases of influenzal pneumonia. All these cases showed high fibrin levels. The average of their series was 1,046 mg of fibrin per hundred cubic centimeters of plasma or 498 mg of fibrin per hundred cubic centimeters of blood. All of these cases were fatal. Gram<sup>4</sup> (Table 34) reports twenty-two determinations on patients with influenzal pneumonia with the average reading of 620 mg of fibrin per hundred cubic centimeters of plasma or 370 mg of fibrin per hundred cubic centimeters of whole blood. He also reports, in Table 16 of his paper, seven determinations on cases with lobar pneumonia with an average plasma fibrin of 1,050 mg per hundred cubic

TABLE 9—Fibrin Values in Four Cases of Lobar Pneumonia

Duration of Dis- ease, Days	Tem- pera- ture, F	White Blood Cells	Hemato- crit Red Blood Cells, per Cent	Fibrin			Remarks
				Average Two Determi- nations, Mg	100 O c Plesma, Mg	100 O c Blood, Mg	
E M	Lobar pneumonia	Type I, complicated by empyema					
5	103	2,400	47	13.0	789	411	100 c.c. Type I serum intravenously
6	103	3,500	47				180 c.c. Type I serum intravenously
7	101	3,700	43	10.6	610	364	180 c.c. Type I serum intravenously
8	99.4	2,400	44	8.7	535	297	
9	100.4	2,500	44	7.0	425	238	
11	99.6	2,300	44	8.9	535	295	Cough, chest pain
13	100.6	2,000	41	8.5	500	294	Fluid signs in chest
14	99.6		43	9.1	544	310	
15							600 c.c. fluid withdrawn
Case W M							
3	104 rectal	17,000	48	17.8	1,083	565	
4	105 rectal	20,000	45	10.4	645	354	Clinically much improved
Case E M							
9	100.5	2,300	51	16.6	1,050	519	Atypical Type II pneumococcus, tubercle bacilli found in sputum
11	102.4	3,300	50	7.3	450	225	Temperature on three previous days below 100
17	100	2,800	57	9.6	620	264	Temperature 101 next day
21	99.6	1,400	37	6.5	385	244	Patient comfortable, but very weak
Case W M							
Post crisis 98.6			50	7.05	438	219	Blood chlorid normal 2/6/21
			47	5.6	339	179	2/9/21

centimeters or an average whole blood fibrin of 610 mg per hundred cubic centimeters. All workers have found a high blood fibrin during the active stage of lobar pneumonia.

In the present study, the blood fibrin rapidly dropped to a normal or nearly normal level following an uncomplicated crisis. Any complication, such as empyema accompanied by fever, caused the fibrin level to rise again. It will be noted that the fibrin curve and the white blood cell curve did not run parallel in all instances.

Table 9 gives the results obtained in one case of Type 1 pneumococcus pneumonia and three cases of Type 2 pneumococcus pneumonia.

## FIBRIN VALUES IN A MISCELLANEOUS GROUP OF DISEASES

Table 10 gives the results of fibrin determinations on a miscellaneous group of patients. Only four cases of this group had fibrin values below normal. These were patients with splenic anemia, cirrhosis of the liver, interstitial hepatitis (syphilitic), and severe secondary hemorrhage.

## SUMMARY

1 The average *blood* fibrin for normal men was found to be 163 mg per hundred cubic centimeters, for normal women, 179 mg per hundred cubic centimeters. Variations of 25 mg above or below these

TABLE 10—Fibrin Values in a Miscellaneous Group of Diseases

Disease	Fibrin			Remarks
	Per 100 C c Plasma, Mg	Per 100 C c Blood, Mg	Red Blood Cells, per Cent	
Cirrhosis	435	272	35	
Cirrhosis	435	236	49	Ascites
Alcoholic cirrhosis	380	226	40	Temperature 100
Cirrhosis	236	113	52	
Interstitial hepatitis	233	146	37	Syphilitic
Malignancy of pancreas	570	302	47	Jaundiced
Chronic obstructive jaundice	505	298	41	
Metastatic carcinoma of liver	356	222	38	
Carcinoma of stomach (?)	800	545	38	Greatly enlarged liver
Splenic anemia	212	131	39	
Splenic anemia	480	385	19	
Secondary anemia	243	155	36	
Hemophilia	530	370	30	
Polycythemia	423	76	?	
Postdysarsenal jaundice	624	358	42	
Postdysarsenal jaundice	415	207	50	
Postdysarsenal jaundice	535	172	68	Died of pneumonia
Syphilis	443	212	52	Visceral
Syphilis	472	200	57	Visceral
Syphilis	305	202	49	Nerve
Syphilis	459	227	50	Nerve
Syphilis	432	220	49	Nerve
Pneumonia	1,083	565	48	Type II, third day of disease
Pneumonia	1,050	519	51	
Pneumonia	438	219	50	Posterioris
Pneumonia	789	417	47	
Encephalitis	333	153	54	
Encephalitis	440	211	52	
Pyelitis	715	372	48	Probable bronchopneumonia
Septic wound	635	420	34	
Typhoid	615	284	54	

figures may be said to be within normal limits. The average *plasma* fibrin found for normal men was 332 mg per hundred cubic centimeters, for normal women, 344 mg per hundred cubic centimeters. Variations of 50 mg above or below these figures are probably within normal limits.

2 The average blood fibrin of *pregnant women* was found to be 273 mg per hundred cubic centimeters, the average plasma fibrin, 415 mg per hundred cubic centimeters. These figures will probably be found to hold true for the last months of pregnancy only.

3 *Toxemia of pregnancy* (nonfatal) is associated with an elevated blood fibrin. The elevation seems to parallel the severity of the symp-

toms The toxic manifestations due to nephritis complicating pregnancy are not accompanied by a marked fibrin elevation It is inferred from the difference in fibrin reaction that the toxic syndrome due to nephritis complicating pregnancy is of a different nature than that of true toxemia of pregnancy

4 Two fatal cases of *acute liver atrophy* were associated with a low blood and plasma fibrin content

5 Nonfatal *arsphenamin jaundice* was associated with an elevated blood and plasma fibrin It is inferred from necropsy material and by comparison with cases of catarrhal jaundice that it is the liver parenchyma and not the bile ducts that are diseased in this condition

6 Lobar pneumonia was associated with a greatly elevated blood fibrin The fibrin rapidly falls to normal after uncomplicated crisis Complications (e g, empyema) cause a subsequent fibrin rise The fibrin curve does not parallel the white blood cell count in all instances

7 A series of fibrin determinations on a miscellaneous group of diseases is tabulated

# STUDIES IN FUSIFORM BACILLI AND SPIROCHETES

## IX THEIR RÔLE IN PULMONARY ABSCESS, GANGRENE AND BRONCHIECTASIS <sup>1</sup>

ISADORE PILOT, M D, AND D J DAVIS, M D

CHICAGO

In a study of infections with the fusiform bacillus and spirochetes, an exceedingly important group were the lesions in the lungs in which these micro-organisms were found. The following report is the result of a combined clinical and pathologic study of thirty-seven cases of fusospirochete pulmonary infections. It is hoped that this study will clarify certain hitherto obscure pulmonary infections, particularly those characterized by abscess formation and gangrene, and establish these infections as a definite clinical entity, comparable to the pneumonic processes caused by the pneumococcus, streptococcus and tubercle bacillus. In previous studies <sup>1</sup> the association of fusiform bacilli and spirochetes in putrid and gangrenous lesions of the body was emphasized, particularly in connection with such processes about the teeth, tonsils, middle ear, lungs and genitalia. At that time it was pointed out that these organisms were important etiologic agents in certain types of pulmonary lesions, characterized by necrosis and foul expectoration. We have conducted further investigations in these interesting but imperfectly understood pulmonary conditions. It was stated that these processes were often the result of lowered resistance in locations where these organisms normally reside or can readily enter. In connection with the respiratory lesions, the infections appear to arise largely from the organisms that reside in the mouth and upper respiratory passages.

About the teeth, these organisms were among the first to be recognized as normal inhabitants. They are especially numerous in heavy tartar deposits and about carious teeth and diseased gums. The tartar, when examined fresh, presents brushlike processes having central strands with coccoid and fusiform bodies arranged about the terminals <sup>1</sup>. Smears reveal large numbers of coarse and fine spirochetes, fusiform bacilli of various types, leptothrix filaments, and gram-positive streptococci. Anaerobically, the fusiform bacilli produce a putrid odor in tissue media. The streptococci are usually of the viridans type, only occasionally of the hemolytic variety.

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<sup>1</sup> From the Department of Pathology and Bacteriology, University of Illinois College of Medicine.

<sup>1</sup> Davis, D J, and Pilot, Isadore. Studies of *Bacillus Fusiformis* and Vincent's Spirochetes, J A M A **79** 944-951 (Sept 16) 1922.

In the faucial tonsils, we first noted these organisms in large numbers in the granular masses lying in the crypts, which in their appearance are like actinomyces granules. These bodies are found in 30 per cent of extirpated tonsils and at some time are probably present in all individuals. They appear as foul, gray or yellow, single or multiple granules, from 1 to 6 mm in diameter, lying in the depths or near the mouths of the crypts from which they may be expressed. Microscopically, they are made up of filaments arranged in ray-like structure not unlike actinomyces but containing no true branching threads. Filamentous organisms form a central shaft, about which small comma-shaped, fusiform and large diplococcoid bodies are arranged perpendicularly. Throughout are enormous numbers of fusiform bacilli and spirochetes together with diplococci. The spirochetes are gram-negative and actively motile. The cocci are chiefly streptococci of viridans or hemolytic type, the former often anerobic in early cultures. The bacilli are demonstrable in smear or culture in 80 per cent of extirpated tonsils.<sup>2</sup> It would seem that a process similar to that of tartar formation occurs in the tonsil with the formation of spherical structures in the crypts instead of a film. In the nasopharynx, the fusiform bacilli are found in 32.6 per cent and spirochetes in 5 per cent.<sup>2</sup>

#### PATHOGENICITY OF THESE ORGANISMS

It is not surprising, therefore, that with these organisms normally about tonsils and teeth that under certain conditions these bacteria find their way to the lower respiratory tract and give rise to definite lesions. In the extensive literature on pulmonary abscess and gangrene, only a few authors have noted the bacteria associated with or underlying these conditions. For the most part, the general impression was held that the ordinary pyogenic organisms such as staphylococci, streptococci, *B. influenzae* and pneumococci were largely responsible, occurring in mixed flora. Little attention has been paid to the possible existence of certain anerobes as important etiologic agents.

Rona<sup>3</sup> reported two cases of pulmonary gangrene in which fusiform bacilli and spirochetes occurred.

Feldman<sup>4</sup> found spirochetes at the margin of the necrotic wall in pulmonary gangrene.

Budav<sup>5</sup> observed fusiform bacilli and spirochetes of various types in histologic studies of gangrene and abscess in thirty-five cases.

<sup>2</sup> Pilot, I., and Brams, J. Studies of Fusiform Bacilli and Spirochetes IV. Occurrence in Tonsils and Adenoids, *J. Infect. Dis.* **33** 134-138 (Aug) 1923.

<sup>3</sup> Rona. *Arch. f. Dermat. u. Syph.* **74** 171-201, 1905.

<sup>4</sup> Feldman. *Wien. klin. Wchnschr.*, 1906.

<sup>5</sup> Budav. *Beitr. z. path. Anat. u. z. allg. Path.* **48** 70-122, 1910.

Arnheim<sup>6</sup> found spirochetes identical with dental spirochetes in five cases of pulmonary gangrene

In this country a few isolated observations were made by Fishberg and Kline<sup>7</sup> who reported two cases, and by Kline and Blankenhorn<sup>8</sup> who recently described four other cases. The observations made heretofore would make one believe that these lesions are rare, but our experience has shown that they are not uncommon.

The factors that determine such infection correspond to a large extent to those associated with pulmonary abscess and gangrene. Earlier works emphasized pneumonia as an etiologic agent. While we still meet these complications in pneumonia, the number of such cases is small compared to the total number observed. A far more important cause today is general anesthesia, particularly since operative procedures are performed much more frequently and tonsillectomy is greatly in vogue. In a few instances, infection in the form of abscess or gangrene is superimposed on certain pathologic lung states, such as bronchitis, bronchiectasis, tuberculosis and carcinoma, vascular changes in lungs such as infarction and diabetes may occasionally be the predisposing factor. Foreign bodies, perforating lesions into bronchi may carry the infection into the lungs. In not a few instances the underlying predisposing factor is not demonstrable.

The association of these anaerobes morphologically and culturally similar to those found about the teeth and tonsils in necrotic lesions of the mouth and in the lung would indicate that these organisms, while saprophytic under normal conditions, may become pathogenic agents. Because of this behavior, we prefer to refer to these organisms as opportunists. Their pathogenicity, however, is low, requiring in the experimental animal relatively large doses to produce lesions. The fusiform bacillus in pure culture has very little pathogenicity. Injected into the pleural cavity of the rabbit in large doses, little reaction aside from slight fibrinous exudation occurs. For the production of a putrid lesion, the addition of a pyogen, particularly the streptococcus, is necessary. The cocci when injected alone produce a serofibrinopurulent pleuritis with no odor. When spirochetes, fusiform bacilli and cocci are combined the lesion is putrid. The pathogenicity of such mixtures was determined by injecting macerated granules of the tonsils and tartar deposits which showed such organisms in smear and culture, intrapleurally into rabbits. A putrid empyema resulted in a few days,

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6 Arnheim Zentralbl f Bakteriologie u Parasitenk **19** 20-34, 1911

7 Fishberg, Maurice, and Kline, B. S. Spirochetal Pulmonary Gangrene, Arch Int Med **27** 61 (Jan) 1921

8 Kline, B. S., and Blankenhorn, M. A. Spirochetal Pulmonary Gangrene, J A M A **81** 719-723 (Sept 1) 1923

*Infection Observed in Patients Aged from Eight to Seventy Years*

Case	Age	Sex	Color	Predisposing Factors	Pulmonary Lesion	F	Bacteriology	Termination	Therapy
1	18	♀	W	Tonsillectomy, nitrous oxid anesthesia	Abscess right upper lobe	F	fusiformis, spirochetes, Streptococcus viridans	Recovery gradual	3 doses neo arspheuanum.
2	10	♂	C	Tonsillectomy, ether anes thesia	Abscess, right middle lobe	B	fusiformis, spirochetes, coel	Recovery gradual, spontaneous	
3	24	♂	W	Tonsillectomy, ether anes thesia	Abscess	B	fusiformis spirochetes, streptococci	Sudden rupture recovery	
4	10	♂	W	Tonsillectomy, ether anes thesia	Abscess, left lower lobe	B	fusiformis, spirochetes, Streptococcus viridans	Sudden rupture recovery	
5	41	♀	W	Tonsillectomy, ether anes thesia, subacute arthritis and endocarditis	Multiple abscess, both lungs	B	fusiformis, Streptococcus hemolyticus	Death	
6	28	♀	C	Hysterectomy, ether anes thesia	Abscess, right lower lobe	B	fusiformis, spirochetes, streptococci	Recovery spontaneous	
7	32	♂	W	Appendectomy, ether anes thesia	Gangrene of right lung	B	fusiformis, spirochetes, Streptococcus viridans, B capsulatus (few)	Death	4 doses neo arspheuanum, temporary improve ment only
8	40	♀	C	Hysterectomy, ether anes thesia	Diffuse gangrene, right upper lobe	B	fusiformis, spirochetes, streptococci	Death	
9	48	♂	W	Herniotomy, ether anes thesia	Pulmonary abscess, right upper lobe	B	fusiformis, spirochetes, coel	Improved	6 doses neo arspheuanum
10	53	♂	W	Perforation of esophageal carcinoma	Gangrenous broncho pneumonia, right upper lobe	B	fusiformis, coel, Gram negative bacilli	Death	
11	46	♂	W	Foreign body	Abscess, right lower lobe	B	fusiformis, spirochetes, Streptococcus viridans	Sudden rupture, recovery	
12	16	♂	W	Foreign body, tonsillectomy	Abscess, right lower lobe	B	fusiformis, spirochetes Streptococcus hemolyticus and viridans	?	
13	68	♂	W	Bronchiectasis	Gangrenous broncho-pneumonia, both lungs	B	fusiformis, spirochetes, S hemolyticus (few), S viridans (many), Staphylococcus albus (few), Gram negative bacilli (few)	Death	
14	29	♀	W	Bronchiectasis, pregnancy	Multiple abscess, right middle and lower lobes cerebral abscess	B	fusiformis, spirochetes, S hemolyticus (few), S viridans (many), Staphylococcus albus (few), Gram negative bacilli (few)	Death	
15	29	♂	W	Bronchiectasis, ether anesthesia	Diffuse gangrene of right lung, cerebral abscess	B	fusiformis, spirochetes, S hemolyticus (few), S viridans, S hemolyticus (few) theroids (few)	Death	
16	55	♂	C	Bronchiectasis, perforation of abscess into bronchus	Gangrene of right lung	B	fusiformis, spirochetes, S viridans, B influenzae (few), S hemolyticus (few)	Death	
17	25	♀	W	Bronchiectasis	Bronchopneumonia, Multiple abscesses (?)	B	fusiformis, spirochetes, S hemolyticus and S viridans, Micrococcus catarrhalis (few)	Improved	6 doses neo arspheuanum
18	44	♂	W	Bronchiectasis	Multiple cavities, right lower lobe bronchopneumonia	B	fusiformis, spirochetes, S viridans	Improved, recurrence	6 doses neo arspheuanum

19	50	♂	O	Diabetes	Gangrenous broncho-pneumonia, right lung	B fusiformis, spirochetes, S hemolyticus, pneumococcus (few), S albus (few)	Death	
20	57	♂	W	Pulmonary infarct, cardiac decompensation	Infarction of right lung with gangrene	B fusiformis, streptococci	Death	
21		♂		Bronchogenic carcinoma of lung, bronchiectasis	Gangrenous broncho-pneumonia, right lung	B fusiformis, streptococci, B influenzae	Death	
22		♂		Bronchogenic carcinoma of lung	Multiple putrid abscesses	B fusiformis, spirochetes, S viridans	Death	
23	25	♀	C	Chronic ulcerative pulmonary tuberculosis	Pulmonary gangrene	B tuberculous, B fusiformis, spirochetes, S viridans, M catarrhalis (few)	Death	
24	38	♂	W	Chronic fibrocascous pulmonary tuberculosis	Diffuse gangrene of right lung	B fusiformis, B tuberculous, S hemolyticus, S albus (few)	Death	3 doses neo arspenamin
25	13	♂	C	Tonsillectomy, military tuberculosis of lungs, bronchiectasis	Multiple putrid abscesses, putrid empyema	B fusiformis, spirochetes, S viridans, S albus (few), diptheroids (few)	?	
26	45	♂	W	Chronic ulcerative pulmonary tuberculosis, bronchiectasis	Multiple putrid abscesses	B tuberculous, B fusiformis, spirochetes, S viridans, S albus	?	
27	34	♂	W	Chronic ulcerative pulmonary tuberculosis	multiple abscesses	B tuberculous, B fusiformis, spirochetes, streptococci		
28	38	♀	W	Lobar pneumonia	Multiple abscesses	B fusiformis spirochetes, S viridans, B capsulatis	Improved	Sodium cacodylate
29	30	♂	W	Lobar pneumonia (?)	Putrid abscess of right lower lobe, lobar pneumonia, right upper and middle lobes	B fusiformis, spirochetes, S hemolyticus pneumococcus (few)	Death	
30	52	♂	W	Acute bronchitis (?)	Putrid abscess of right lower lobe	B fusiformis, spirochetes, S hemolyticus (few), S viridans	Recovery	Neo arspenamin
31	50	♂	W	Trauma to chest	Multiple putrid abscesses of left lower lung	B fusiformis, S viridans, staphylococcus (few), M catarrhalis (few)	Improved	7 doses neo arspenamin pneumothorax
32	32	♂	C	Bullet wound of chest	Gangrene, right lung, right putrid pyo-pneumothorax	B fusiformis spirochetes, S viridans	Death	
33	37	♀	W	Fall with fracture of forearm	Multiple putrid abscesses	B fusiformis, spirochetes, S viridans	Death	Surgical
34	32	♂	C	None determined	Multiple gangrenous abscesses of right lung	B fusiformis, spirochetes, S viridans and S hemolyticus	Death	
35	34	♂	C	Urethral stricture ascending pyelonephritis	Gangrenous broncho-pneumonia, both lungs	B fusiformis, spirochetes, S hemolyticus B capsulatis	Death	
36	53	♂	W	None determined	Pulmonary abscess, right lower lobe	B fusiformis, spirochetes, S viridans, S hemolyticus	Improved	2 doses neo arspenamin
37	20	♂	W	"Cold" (?)	Pulmonary abscess, right lower lobe	B fusiformis, spirochetes cocci	Improved	4 doses neo arspenamin

\* In this column, ♀ indicates female ♂ male



and in the pus spirochetes, bacilli and cocci were demonstrable<sup>1</sup> The spirochetes seemed to disappear first, followed by the fusiform bacilli, leaving only the coccal forms The cocci showed an aggressive tendency, advancing to the opposite pleura, into the pericardium and into the general circulation while the others were confined to the injected side The tartar from carious teeth, an emulsion made of membrane from Vincent's angina and the sputum from pulmonary gangrene, produced the same type of reaction Subcutaneously necrotic, sloughing lesions were produced in the guinea-pig by the same material From these observations, it would seem that we are concerned with a combination of organisms which thrive in symbiosis producing in the tissues a constant putrid lesion We must recognize, therefore, that lesions may arise not only from pure cultures of bacteria but also from two or more organisms in symbiosis

Predisposition to fusospirochete infection depends on a multitude of factors, many of which are combined in individual cases As a rule, the patients are not robust, but often undernourished and weakened by other causes Acute respiratory infections may lower the general resistance Diabetic patients are especially susceptible The infection was observed in patients from 8 to 70 years of age in both sexes The colored race appears to be quite susceptible (see table)

Local factors are of the utmost importance Carious teeth and pyorrhea, conditions in which the anerobes may be found in great abundance, were outstanding findings in many patients but are by no means necessarily associated Heavy tartar deposits may occur, while in some the teeth appear to be in good condition The tonsils apparently do not play as important a rôle as the teeth In a few, the crypts were distended with the foul granules rich in anerobes Such tonsils may be responsible particularly for the pulmonary lesion following tonsillectomy

The normal lung does not harbor these organisms In fourteen pairs of lungs, free from any infectious process, no fusiform bacilli or spirochetes were demonstrable In certain abnormal states these bacteria may establish a habitat in the bronchi In bronchiectasis, they may lead a saprophytic existence and be demonstrated in the sputum, although no necrotic process or abscess formation is associated The sputum as a rule in such instances is not foul In old standing chronic bronchitis and in the sputum of bronchial asthma they may also be found, although no odor is produced If patients with these bronchial conditions develop an acute infection of the respiratory tract either from some virulent autogenous or exogenous micro-organism or virus, or if the general resistance becomes decidedly lowered, the saprophytic anerobes often first cause a putrid bronchitis, spread through the

necrotic mucosa into the lung parenchyma, with the production of single or multiple foci of suppuration or gangrene

The diseased parenchyma of the lung is decidedly inclined to become infected secondarily. Malignancy, tuberculosis and pneumonia may be complicated by abscess or gangrene. It is remarkable, however, that the anaerobes only rarely cause superimposed infection in the tuberculous, although the streptococcus, staphylococcus and *B. influenzae* are commonly associated with the tubercle bacillus. Pneumonia of the lobar type is very seldom complicated by fusospirochete infection. Primary carcinoma of the lung, on the other hand, especially the bronchogenic type is often terminated by such secondary infection.

#### POST-TONSILLECTOMY ABSCESS

Inspiration of secretions of the mouth during general anesthesia is a frequent occurrence, particularly in tonsillectomy. In some, even with care, a small amount may be a nucleus for a pulmonary abscess. In others the large quantity or dose aspirated is the chief factor, particularly in children who are in good health.

In our experience the bacteria underlying post-tonsillectomy abscess or gangrene have usually been fusiform bacilli and spirochetes associated with streptococci. The condition manifests itself in a few days following the operation with cough, elevation of temperature (from 101 to 103), increase in pulse rate, general lassitude and polymorphonuclear leukocytosis. Distinct pain in the chest is often felt. Physical findings depend on location of the lesion, and often at this stage are absent or indefinite. From the tenth to the fifteenth day expectoration may come gradually or suddenly with the production of liquid sputum of foul or peculiar sweet odor. Smears made at this period reveal many streptococci, various forms of fusiform bacilli and spirochetes. The spiral forms may vary in number, often occurring sparsely among the more constant bacilli. The streptococci are usually of the viridans type. The expectoration continues for several days or weeks. In those with sudden rupture the condition may clear quickly. In four of the patients this abscess appeared single with recovery of all. In one, the abscesses were multiple, causing death on the eighteenth day. In one, arsphenamin was employed with good results.

The following cases are presented briefly.

#### REPORT OF CASES

CASE 1—A girl, aged 18 years, developed a cough, foul expectoration, and pain in the right chest fourteen days after tonsillectomy under gas anesthesia. Sputum formed three layers and contained numerous fusiform bacilli, spirochetes and streptococci. Her condition during the next two weeks became worse. Roentgen-ray examination revealed a large abscess with a cavity in the right upper lobe (Fig 1). She was given three doses of neoarsphenamin

(0.6 gm) Improvement was immediate after the first dose, with a fall in the temperature and less expectoration. In a roentgenogram, taken four weeks after the first injection, the abscess had disappeared (Fig 2). The patient has remained well for the last eighteen months.

CASE 2—A youth, aged 15, colored, complained of cough, pain in the left chest, fever and foul expectoration about three weeks after tonsillectomy under ether anesthesia. There was expectoration of large quantities of foul, gray-green sputum in which many bacilli, spirochetes and cocci appeared. Physical



Fig 1 (Case 1)—Post-tonsillectomy pulmonary abscess in right upper lobe before neo-arsphenamin therapy

and roentgen-ray examination disclosed an abscess with cavity in the right middle lobe. Expectoration gradually became less, the temperature dropped to normal in the next two days, with fewer physical signs although the roentgenogram still revealed considerable pathologic changes. The patient left the hospital and did not report for subsequent examination.

CASE 3—A man, aged 24, who had tonsillectomy performed under ether anesthesia, developed considerable weakness. While at work two weeks later, he suddenly expectorated a large quantity of foul sputum. A sample revealed numerous spirochetes, fusiform bacilli, and streptococci. Expectoration ceased the next day, recovery was rapid with no further symptoms.

CASE 4—A boy, aged 10, developed a temperature of 102.4 F ten days after tonsillectomy under ether anesthesia. Fever, cough and some pain continued for four days, when suddenly he expectorated 4 ounces (118.4 cc) of foul pus, containing fusiform bacilli, spirochetes and cocci. Physical and roentgen-ray examination presented signs of consolidation and a small amount of fluid in the left lower chest. The temperature dropped and expectoration ceased in twenty-four hours. Examination five weeks later gave no physical or roentgen-ray findings.

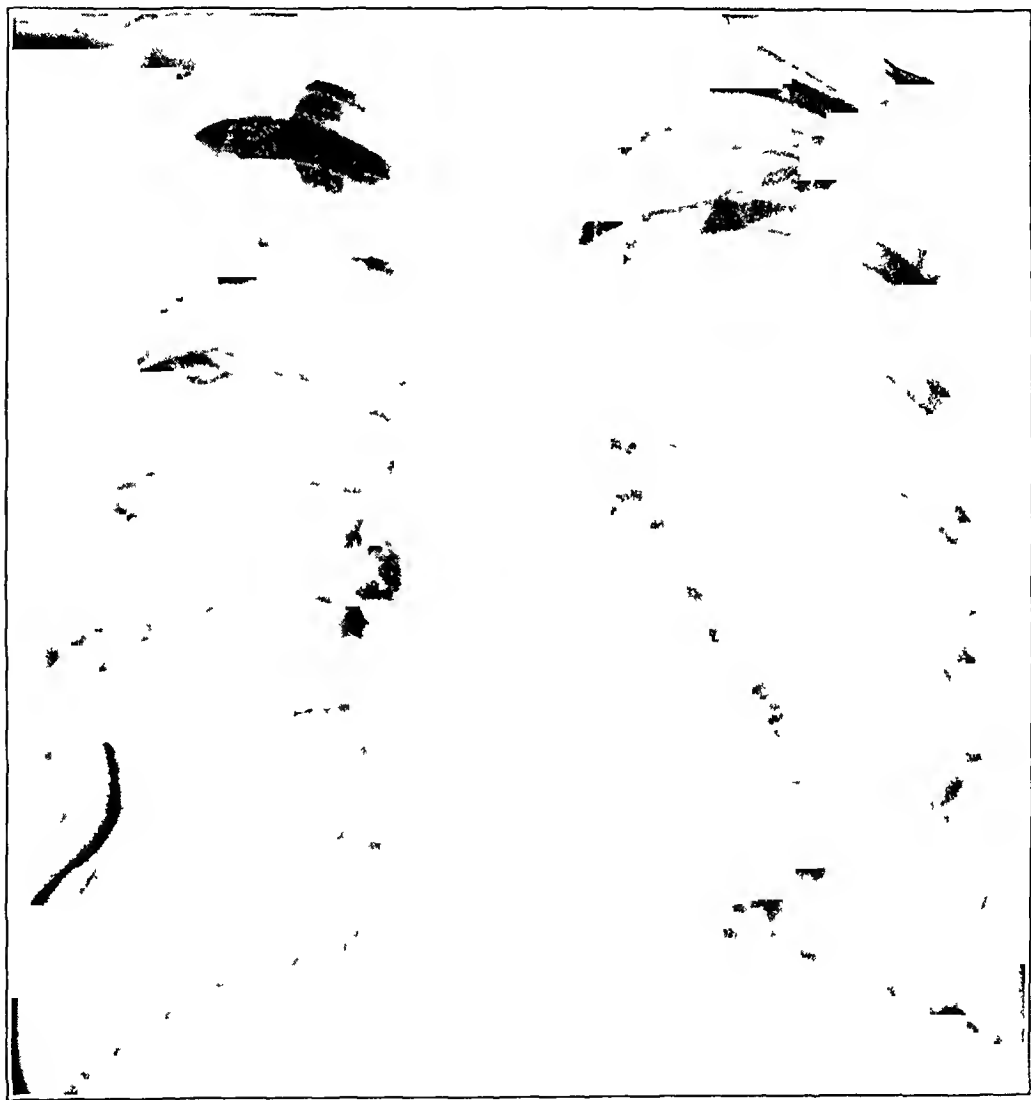


Fig 2 (Case 1) —Post-tonsillectomy abscess after neo-arsphenamin therapy

*Comment*—In Case 4 the abscess discovered on physical and roentgen-ray examination was obscured by the presence of fluid in the pleural cavity. The large amount of pus suddenly evacuated would indicate an abscess of fair size.

CASE 5—A woman, aged 44, was ill for several weeks with subacute polyarthritis and mitral endocarditis. After a normal temperature lasting for two weeks, tonsillectomy was performed. Arthritis recurred immediately. Nine days later she began to bleed from the tonsillar fossa for forty-eight hours. Six days later the temperature rose to 104 and the respirations became labored. Death ensued in three days. Anatomic diagnosis at necropsy was multiple

abscesses of the left lung and right upper lobe (Fig 3) Smears and cultures of pus of necrotic centers of abscesses revealed fusiform bacilli and hemolytic streptococci but no spirochetes

*Comment*—The lesions in the lung were among the earliest observed Beginning necrosis was evident The numbers of bacteria, while considerable, did not compare with the masses seen in older lesions

The mode of infection in post-tonsillectomy pulmonary abscess is largely aspiration of throat secretions The frequency of abscess complicating throat surgery is due to the massive doses of bacteria

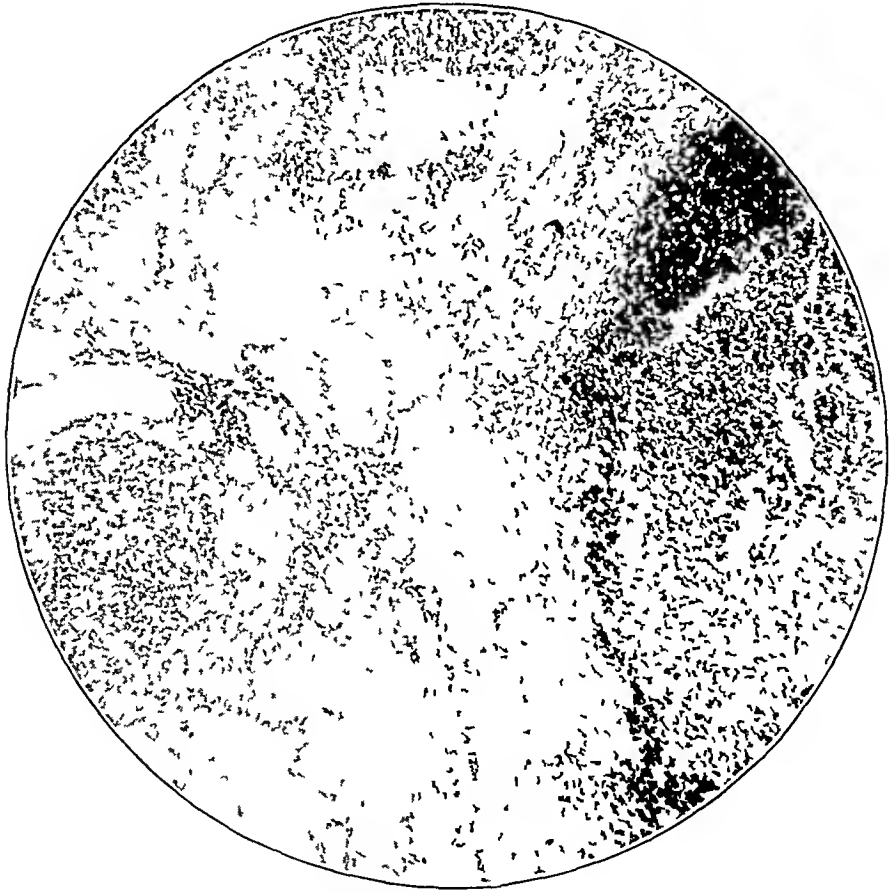


Fig 3—Multiple abscesses following tonsillectomy These were among the earliest lesions observed The centers show beginning necrosis, and in smears revealed fusiform bacilli and cocci in large numbers (hemotoxylin and eosin)

that can be aspirated That aspiration is responsible is further substantiated by the development of abscess and gangrene resulting from ether anesthesia, in which the operative procedure was not in the throat or respiratory tract It is possible that pulmonary infarction may have played a contributory rôle, but in none of the patients clinical symptoms or physical or roentgen-ray findings could be found indicating such complication

In the three cases, pulmonary abscess or gangrene complicated abdominal operation, and in one a herniotomy, all under ether anesthesia. A brief review of these cases is presented.

CASE 6—P. R., a woman, aged 28, colored, had hysterectomy performed under anesthesia for fibroids. Within two weeks she developed clinical and roentgen-ray evidences of pulmonary abscess in the right lower lobe. The sputum was foul and contained fusiform bacilli, spirochetes and streptococci. She made a spontaneous recovery within a month after the onset.

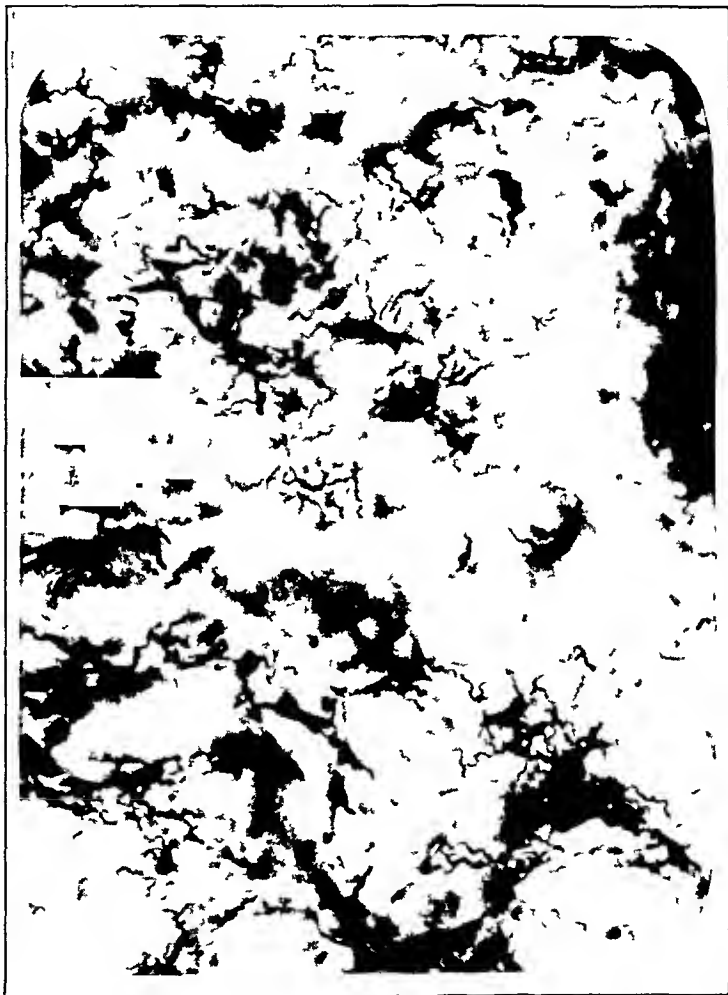


Fig. 4 (Case 8)—Large masses of spirochetes observed in pulmonary gangrene.

CASE 7—J. P., a man, aged 32, developed cough, foul expectoration and fever two weeks after appendectomy under ether anesthesia. Physical and roentgen-ray examination revealed extensive consolidation of the right lung, with the formation of multiple cavities. The sputum was profuse, intensely foul and green. Fusiform bacilli, spirochetes, together with streptococci and gram-negative bacilli were abundant. Neoarsphenamin treatment was started four weeks after onset. Four doses were administered, but only temporary improvement was obtained. Death resulted from toxemia.

CASE 8—L W, a woman, aged 40, colored, developed pain in the chest, cough, bloody expectoration eleven days after hysterectomy under ether anesthesia. Examination revealed extensive consolidation of the right upper lobe. Death occurred in three weeks. At necropsy the anatomic diagnosis was, gangrene of the upper lobe of the right lung, confluent bronchopneumonia of the lower lobe of the right lung. The gangrenous lesions presented in smears and Levaditi preparations enormous numbers of spirochetes (Fig 4), fusiform bacilli, and streptococci. The bronchopneumonia was of the interstitial type (Fig 5).

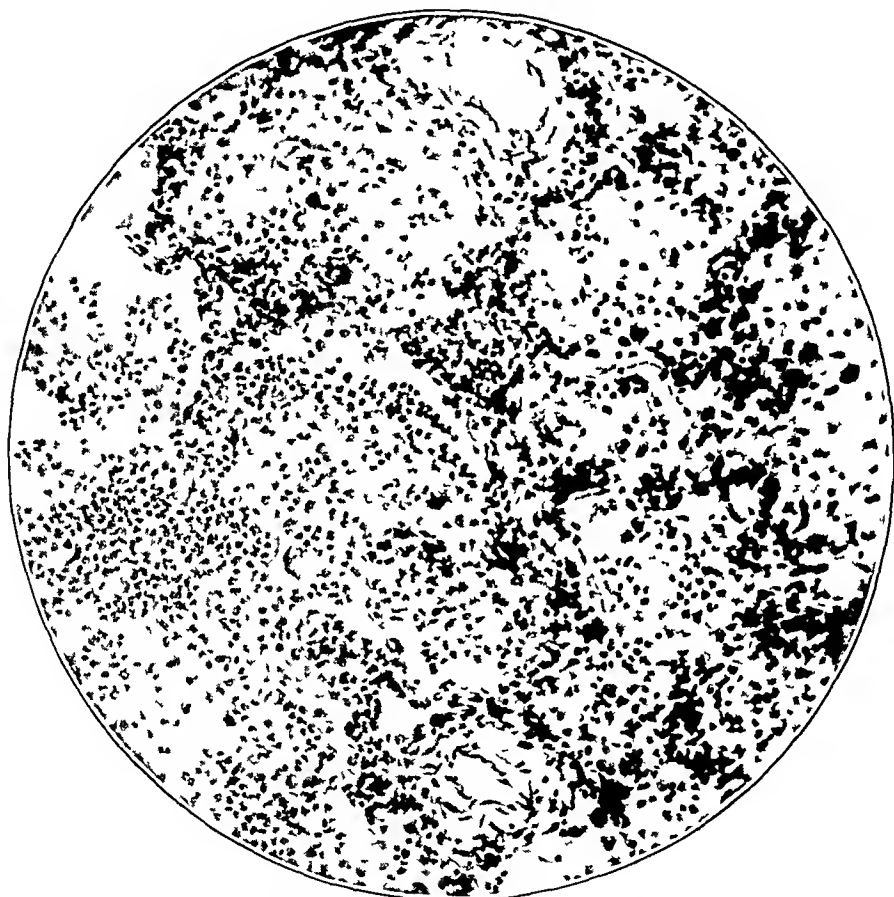


Fig 5 (Case 8)—Interstitial bronchopneumonia associated with pulmonary gangrene. The cells infiltrating the septums were chiefly of the mononuclear type (H and E stain).

CASE 9—S V, a man, aged 48, developed bloody, foul expectoration two weeks after herniotomy under ether anesthesia. Physical and roentgen-ray examination revealed a huge pulmonary abscess in the lower portion of the right upper lobe. The sputum contained cocci, fusiform bacilli and spirochetes. The patient was observed for four weeks, during which time he became worse and the lesion appeared more extensive. Six doses of neoarsphenamin were administered. A decided improvement resulted in four weeks. The temperature was normal, expectoration slight and physical and roentgen-ray signs of the abscess greatly diminished.

Perforating lesions into the trachea and bronchi lead to aspiration of material containing bacteria with the formation of pulmonary

abscesses or gangrenous bronchopneumonia. The bacteria concerned in such lesions are frequently the fusiform bacilli with or without spirochetes. Pulmonary lesions of this sort frequently terminate the clinical course of carcinoma of the esophagus. We have observed that fusiform bacilli and spirochetes of the mouth early infect the ulcerating lesions in the esophagus, causing necrosis with ultimate perforation into the trachea or bronchi and death from the pulmonary complication.

CASE 10—C F, a man, aged 53, complaining of inability to swallow for six months, developed pain in the chest, with cough and expectoration. Examination of the mouth revealed very carious teeth, marked pyorrhea and foul breath. A friction rub occurred over the right lower lobe posteriorly, together with a few moist râles. Blood examination revealed hemoglobin 60 per cent, red blood cells 3,310,000, leukocytes 13,500. Wassermann blood test was negative. The patient died about two weeks after the development of the pulmonary symptoms. At necropsy a primary carcinoma of the esophagus with a fistula leading into necrotic cavity of the right upper lobe was seen. The abscess cavity was foul smelling and gray-green. In smears many fusiform bacilli were found, together with cocci and short gram-negative bacilli. The middle and right lower lobe were involved in an acute bronchopneumonic consolidation. Levaditi sections revealed large numbers of typical fusiform bacilli and cocci in the gangrenous areas and short bacilli plus cocci in the nongangrenous foci. The esophageal mass was a typical squamous cell carcinoma with considerable necrosis.

Infections with these organisms associated with foreign bodies in the lung is illustrated in the following two instances.

CASE 11—C C, a man, aged 46, complained of pain in the right chest, cough, "fever and chills" occurring irregularly for five months. He had been entirely well until one day he felt that a "piece of meat" was sticking high up in the chest. He developed a cough, with slight expectoration and pain in chest about two weeks later. Examination revealed a well nourished man. The teeth were carious and associated with pyorrhea of moderate severity. In the chest there was flatness over the right lower lobe, with diminished fremitus and breath sounds. The temperature varied from 101 to 103, the pulse from 100 to 120. The leukocyte count was 23,400 per cmm. With the roentgen ray, a dense shadow with fuzzy upper border was demonstrated in the right lower chest (Fig 6). One ounce (30 cc) of serofibrinous fluid was removed from this region which in smear revealed a few short chains of streptococci. Four days later, during a spasm of coughing, the patient suddenly expectorated a large amount of foul green pus together with an irregular piece of cancellous bone 6 mm in diameter. The sputum revealed many fusiform bacilli, few spirochetes and streptococci. The temperature dropped to normal the following day, and physical signs of involvement rapidly disappeared in the following week.

*Comment*—It is possible that the bone tissue from a chop was accidentally aspirated into the trachea, but more probably it was swallowed and arrested in the esophagus with subsequent ulceration into the lung.

CASE 12—A J, a youth, aged 16, complained of cough and putrid expectoration. The onset dated three years previously when he developed pain in the right lower chest, cough, and foul expectoration shortly after tonsillectomy. On



examination at that time there was dulness, moist rales and rhonchi over the right lower lobe. In the roentgen-ray film a foreign body was seen in the right bronchus. Bronchoscopy was performed and a small piece of wire 2 cm long was extracted. No decided improvement followed until an artificial pneumothorax was performed. He returned, however, about a year later with recurrence of symptoms and physical signs. At this time sputum was obtained. It was intensely fetid and formed three layers. Tubercle bacilli were not found. Large numbers of fusiform bacilli, long chains of cocci and moderate numbers



Fig 6 (Case 11)—Lung abscess in right lower lobe with serofibrinous pleuritis associated with foreign body

of short slender and long coarse spirochetes were demonstrated. In cultures the colonies were predominantly *Streptococcus viridans* type with a few *Streptococcus hemolyticus*. The patient did not return for further observation.

Abscess and gangrene occasionally complicate other pathologic processes in the lung. In bronchiectasis, the anerobic bacteria are largely responsible.

CASE 13—A man, aged 68, entered the hospital and died on the same day. A history of cough and expectoration for several years had been present. He became decidedly worse six weeks previously. The sputum was green and had a foul odor, no tubercle bacilli were found. At necropsy the anatomic diagnosis was Diffuse bilateral bronchopneumonia with multiple foci of gangrene in both lungs, chronic diffuse bronchitis with moderate bronchiectasis, atrophic pulmonary emphysema, hyperplasia of the peribronchial lymph glands. In the right lung fibrin exudate occurred over the pleura of the lower lobe which was of doughy consistency with firm nodules. Section revealed two confluent cavities in the lower lobe filled with foul, dark, purulent material. Solid raised foci were seen throughout. The left lung presented similar cavities at the base with a small cavity in the apex but no caseous nodules.

Cultures of gangrenous areas gave many colonies of *Stieptococcus viridans*, a few of *Stieptococcus hemolyticus*, *Staphylococcus albus* and small gram-negative bacilli. In the anerobic slants straight and thread forms of *B. fusiformis* occurred.

Microscopic sections presented an interstitial bronchopneumonia with areas of necrosis in places made up of pus cells, debris and bacteria. Levaditi preparations showed many cocci, fusiform bacilli and spirochetes in the necrotic areas.

In the Cases 14 and 15 the bronchiectasis was associated with fusospirochete infection, with complication of metastatic brain abscess.

CASE 14—A woman, aged 29, complained of inability to move the left arm, defective speech, headache and vomiting for three weeks. For two years she had had cough, with some loss of weight. Prior to the development of the cough, she had had an appendectomy, but any direct relation of respiratory symptoms to the operation could not be ascertained. Examination revealed a well-nourished woman in the sixth month of pregnancy. The chest presented impaired resonance, amphoric breathing and moist râles over the right lower lobe. Clubbing of fingers and toes was marked. The left arm was flaccid, and bilateral Babinski sign was present. The Wassermann blood and spinal fluid tests were negative. Globulin was found in the spinal fluid. The sputum was very foul, no tubercle bacilli were found. Blood analysis showed 65 per cent hemoglobin, 3,250,000 erythrocytes, 6,800 leukocytes, with normal differential count. In the roentgen-ray plate multiple small bronchiectatic cavities were demonstrable in the right lower lobe. The temperature was 98.2 F, the pulse 78, respiration 22, blood pressure, systolic 94, diastolic 62.

The patient developed repeated convulsions and died nine days after admittance. At necropsy the anatomic diagnosis was Multiple bronchiectatic cavities and abscesses of lower and middle lobe of right lung, abscess of right cerebral hemisphere, cloudy swelling of parenchymatous organs, 6 months old fetus in uterus.

The right pleural cavity was completely obliterated by firm, fibrous adhesions. The lung was consolidated in scattered areas in the middle and lower lobes. On cut section, numerous abscess cavities, from 2 to 4 cm in diameter, filled with foul smelling pus were present in all lobes, but most numerous about the hilum, where considerable fibrosis was also observed (Fig 7). The bronchi were thickened and the mucosa necrotic in places.

The brain weighed 1,400 gm. Over the right parietal lobe was an area of localized meningitis. One centimeter underneath was a soft area, which on section proved to be a putrid grayish green abscess measuring 8 cm in its anteroposterior and 5 cm in the transverse and vertical diameters involving the cortex. The wall of the abscess was necrotic, and the blood vessels in these regions were dilated (Fig 8).

Smears and cultures from several abscess cavities of the lung revealed typical and filamentous forms of *B. fusiformis* various types of spirochetes.



Fig 7 (Case 14) —Putrid abscesses complicating bronchiectasis



Fig 8 (Case 14) —Putrid cerebral abscess complicating putrid bronchiectasis

*Streptococcus hemolyticus* and small numbers of pneumococci, *Staphylococcus albus*, and diphtheroids. In the brain abscess, cocci, and fusiform bacilli, but no spirochetes were found (Fig 9)

Microscopic section of the brain revealed meninges thickened from exudate of pus cells, extending along the pia to the abscess. The wall of the abscess was made up of granulation tissue with an inner necrotic layer consisting of debris, bacteria and pus cells, and an outer layer of fibroblastic tissue infiltrated with lymphocytes and endothelial leukocytes. In Levaditi stains, cocci and fusiform bacilli but no spirochetes were found in the abscess wall.

*Comment*—The pregnancy may have been an important predisposing factor. The chronic fusospirochete infection may become a severe generalized process, as in pulmonary tuberculosis.

CASE 15—N. C., a man, aged 30, complained of weakness in the right arm and leg for three weeks. Two months previously, under general anesthesia, he was

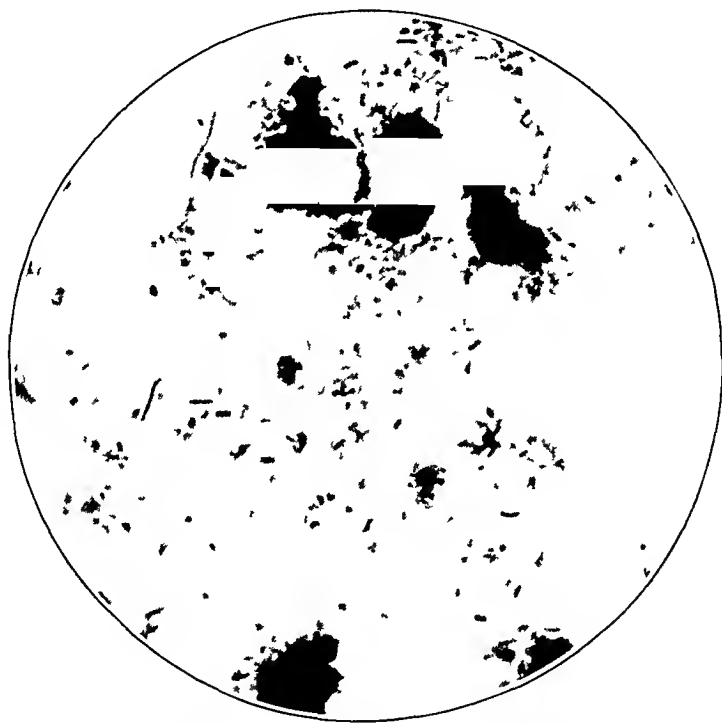


Fig 9 (Case 14)—Smear from pus of cerebral abscess. Fusiform bacilli, cocci but no spirochetes are present.

operated on for subcutaneous abscess in the loin. While in the hospital it was noted that the patient coughed and expectorated large quantities of foul sputum. On physical examination, a right sided hemiparesis was noted. In the chest, impaired resonance and moist râles occurred over the right lung. A homonymous hemianopsia appeared, followed by the development of paralysis of the palate. The spinal fluid was under increased pressure, globulin was present, and cell count 200 per cubic millimeter. The Wassermann test was negative. The anatomic diagnosis at necropsy was as follows:

Extensive gangrene of the right lung, bronchiectasis of the right lung, cerebral abscess of the right parieto-occipital region, localized pachymeningitis, cloudy swelling of parenchymatous organs, right sided fibropurulent pleuritis, hyperplasia of tracheobronchial lymph glands, recent healed scar over the right lumbar quadrant of the abdomen, fibrous periappendicitis and perisplenitis.

The right pleural cavity contained yellow turbid fluid with fibrin, which on culture gave hemolytic streptococci. The right lung on section revealed the

necrotic upper lobe with a cavity 12 by 7 by 7 cm. The remainder of the lung was solid, of green color excepting the middle lobe which was involved in patches. The lining bronchi were covered by foul smelling brown purulent exudate. A few nongangrenous areas were gray, firm and elevated containing yellow pus. The left lung presented scattered areas of consolidation in the form of nodules, from 6 to 10 mm in diameter. The left hemisphere of the brain contained an abscess 1.5 cm in diameter filled with foul smelling pus. The surrounding brain substance was soft and yellow. Cultures of the spinal fluid revealed hemolytic streptococci.

In smears from gangrenous areas of the lung, enormous numbers of fusiform bacilli, spirochetes and cocci were seen, in bronchopneumonic areas the same bacteria in fewer numbers were found. Cultures revealed the predominance of *Streptococcus viridans*, a few hemolytic streptococci and small gram-negative bacilli (*B. influenzae*).

Microscopic section presented the walls of the bronchiectatic cavities lined by granulation tissue. The epithelium was ulcerated, and the underlying tissue infiltrated with round cells. Bronchopneumonic consolidated areas comprised alveoli, some of which were filled with serum, others with polymorphonuclear leukocytes, alveolar epithelium and fibrin. The interstitial tissue was infiltrated with lymphocytes. Other portions of the lung were made up completely of necrotic areas with large masses of blue staining tissue consisting of large masses of bacteria, pus cells, fibrin and necrotic tissue elements, lying free in the lumen. Many of the larger vessels were thrombosed, while the capillaries appeared engorged. Necrosis occurred in bronchial mucosa and large masses of bacteria filled the lumen.

In Levaditi preparation, the necrotic areas of the lung were composed of enormous numbers of bacteria. The bacilli were often comma shaped, others typical fusiform straight and curved. The spirochetes were most numerous at the margin of the necrotic mass and appeared to invade the neighboring regions through the interstitial tissue accompanied by few or no bacilli, and an occasional diplococcus. Some spirochetes were short and fine, others longer and coarser. The lumen of the bronchi contained similar organisms which occurred also in large numbers in the necrotic ulcers of mucosa. In the distant bronchopneumonic areas only cocci were seen.

The brain presented an abscess with the wall made up of an inner layer of lymphocytes and plasma cells and an outer layer of fibroblasts. The cellular infiltrate extended to the cortex. Moderate perivascular infiltration occurred. In Levaditi stains fusiform bacilli, cocci, but no spirochetes appeared in the abscess wall.

*Comment*—General anesthesia undoubtedly lowered the resistance of the lung already bronchiectatic. That complication of fusospirochete gangrene often depends on multiple predisposition factors is well illustrated by this case.

In the next instance, the bronchiectasis was complicated by multiple abscesses with rupture into bifurcation of the trachea.

CASE 16—E. M., aged 55, colored, complained of cough, foul expectoration, pain in the right lower chest with general symptoms of loss of weight and general weakness for three weeks. Physical examination showed dullness in the right upper lobe and a few râles throughout the right lung. The temperature varied from 99 to 101. The leukocyte count was 20,000 with differential count of 88 per cent polymorphonuclear, 9 per cent small mononuclear, and 3 per cent large mononuclear leukocytes. Sputum, which was foul and green, was repeatedly examined for tubercle bacilli with negative results. In smear, fusiform bacilli, spirochetes and cocci were abundant. Cultures demonstrated small gram-negative bacilli (*B. influenzae*), *Streptococcus viridans* and pleomorphic forms of fusiform bacilli.

Neo-arsphenamin (0.45 gm) was administered but the patient was already desperately ill and succumbed two days later.

At necropsy the anatomic diagnosis was

Multiple gangrenous abscesses in the right upper and lower lobe, gangrenous tracheitis, bronchiectasis of the right lung and right pyothorax, caseous tuberculosis of the peribronchial lymph gland, perforation of the trachea at bifurcation.

The ulceration through the trachea was accompanied by extensive peritracheal necrosis and gangrene of the adjoining pleura and lung. The mucosa at this point was green and necrotic. The right pleural cavity contained blood tinged foul smelling pus. The pericardial cavity contained 100 cc of fluid with a few fibrin flakes. The right lung presented numerous small abscess cavities in the apex and right lower lobe from 1 to 2 cm in diameter. The middle lobe and left lung on section revealed a few raised areas of bronchopneumonia. In microscopic section the cavities were bronchiectatic, lined by granulation tissue consisting of round cells, young vessels and fibroblasts. Large areas of total necrosis were seen. In these regions the blood vessels were thrombosed. Alveoli were filled with exudate of fibrin, polymorphonuclear leukocytes and desquamated epithelium in the bronchopneumonic areas. Mucosa of the bronchi was necrotic and masses of bacteria occurred in the poorly stained areas.

Levaditi preparations showed many fusiform bacilli, a few spirochetes and many cocci in necrotic areas and margin of abscess wall.

In two patients with bronchiectasis the complicating fusospirochete infection was treated with neo-arsphenamin with favorable results.

CASE 17—V, a woman, aged 25, complained of cough and expectoration of large amount of foul sputum over a period of fourteen years. Prior to onset she had had empyema and a rib resection. Physical examination showed a patient, underweight, with many carious teeth, moderate pyorrhea and foul breath. In the chest impaired resonance and bubbling râles were found in the right lower lobe. Blood showed 84 per cent hemoglobin, 4,560,000 erythrocytes per cubic millimeter, and 12,600 leukocytes with a differential count of 81 per cent polymorphonuclear neutrophils, 3 per cent basophils, 1 per cent eosinophil, 15 per cent small lymphocytes, and 1 per cent large mononuclear. The Wassermann reaction was negative. Sputum varied from 6 to 8 ounces (from 178 to 236 cm) daily, forming three layers. Smears revealed cocci, fusiform bacilli and spirochetes. In cultures *Streptococcus hemolyticus*, *Streptococcus viridans*, *Micrococcus catarrhalis* appeared. Roentgen-ray film showed increase in the hilum shadow with small bronchiectatic cavities in the right lower lobe near the hilum. Six doses of neo-arsphenamin (from 0.45 to 0.6 gm) were administered intravenously. The odor of the sputum disappeared, the quantity diminished, and smears revealed fewer fusiform bacilli and complete absence of spirochetes. The râles in the chest were fewer, in the roentgen-ray film, however, little change was noted.

CASE 18—R. M., a man, aged 44, entered with a history of expectoration beginning seventeen years ago. Previously he had had pleurisy and pneumonia complicated by an abscess of the hip, and later by considerable cough and expectoration. He improved in a few months and was comparatively free from symptoms for six years. Profuse expectoration returned and continued for nine months. Up to four months prior to entrance to hospital he was in good general health except for an occasional paroxysm of cough and expectoration. For the last four months the expectoration was foul and often blood streaked. He improved after a brief stay, receiving three doses of neo-arsphenamin but returned about ten weeks later with very foul expectoration.

Examination then presented an undernourished adult white man with very foul breath. The teeth were covered with heavy tartar deposits. In the chest impaired resonance, increased vocal and tactile fremitus and cavernous breathing were found over the right lower lobe. Some moist, sibilant and sonorous

rales were scattered over the entire chest. The blood Wassermann was negative. Hemoglobin, erythrocyte and leukocyte counts were normal. The sputum formed three layers, was of a foul odor and revealed many cocci, fusiform bacilli and a moderate number of spirochetes. In cultures, the cocci appeared as pure *Streptococcus viridans*. A clinical diagnosis of bronchiectasis complicated by pulmonary abscess was made. Three doses of neo-arsphenamin (0.3, 0.5 and 0.6 gm) were given. The odor and amount of expectoration were considerably reduced.

*Comment* (Cases 50 and 29)—It is, of course, obvious that neo-arsphenamin is no cure for bronchiectasis, but if the medication can control or diminish the putrid expectoration, it is certainly of great benefit to such patients.

Vascular changes and lowered resistance in a diabetic patient predispose to fusospirochete infection, with resulting pulmonary gangrene.

CASE 19—H. H., a man, aged 50, colored, complained of pain in the right chest, cough and profuse expectoration of foul green sputum for one month. For two years he had been aware of being a diabetic patient with typical symptoms of thirst, polyuria and weakness. Loss of weight became pronounced in the last three months. One year previously, he had noted numbness of the lower extremities especially of the feet. Urinary obstruction occasionally necessitated catheterization.

On examination, the patient appeared emaciated. The teeth were artificial, the breath foul. The chest presented dullness, diminished fremitus and breath sounds, with friction rub over the right lung. The urine contained large quantities of glucose, acetone, diacetic acid and a trace of albumin. The patient became comatose the following day. Glucose, sodium bicarbonate and insulin were administered but death occurred in twenty-four hours.

The anatomic diagnosis at necropsy was as follows:

Confluent bronchopneumonia of the right upper and lower lobe with multiple foci of gangrene. lobar pneumonia of the left middle lobe with gangrenous abscess, diffuse suppurative bronchitis, marked hypostatic edema and congestion of both lungs, acute serofibrinous pericarditis, atrophy of pancreas, copper reducing substance in urine, emaciation, cloudy swelling of parenchymatous organs, acute hyperplasia of tracheobronchial lymph glands, healed tuberculosis of the apex of the left lung, moderate chronic diffuse nephritis, adenomatous hypertrophy in the median lobe of the prostate, hypertrophy of the musculature of the urinary bladder.

The right lung filled the pleural cavity. The pleura over the lower and middle lobe was covered with fibrinous exudate. The upper lobe was firm in the posterior and inferior portion. The middle was completely consolidated. The lower lobe contained irregular confluent nodules in the posterior portion. Section of the upper and lower lobes was grayish red with multiple areas green in color, from 1 to 3 cm in diameter. The middle lobe contained a green abscess cavity 3.5 cm in diameter, filled with foul detritus. The left lung presented a few scattered areas of consolidation in the lower lobe.

Smear made from the necrotic areas showed many types of fusiform bacilli, cocci, but few spirochetes. In cultures *Streptococcus hemolyticus*, few colonies of pneumococcus and *Staphylococcus albus* and pleomorphic forms of *B. fusiformis* were obtained.

Microscopic studies presented a picture of an interstitial bronchopneumonia, with areas of complete necrosis. The bronchopneumonic areas contained alveoli, some filled largely with serum, fibrin, a few polymorphonuclear leukocytes, many alveolar epithelial cells and endothelial leukocytes, others were densely packed with pus cells, fibrin, and debris. The alveolar walls were swollen, and the interstitial tissue infiltrated chiefly with lymphocytes and large mononuclear leukocytes. The cavitations were lined by necrotic tissue consisting of bacterial masses, fibrin, cellular debris and pus cells. Some portions are entirely

necrotic, staining poorly, surrounded by a dense cellular infiltrate. In many of the large vessels thrombosis had occurred and the capillaries appeared engorged.

Levaditi preparations revealed enormous numbers of bacilli and cocci in necrotic areas. The bacilli were typical fusiform, straight and curved, some long and thread-like, and many short comma forms. Few spirochetes occurred in the bacterial masses. At the margin, however, the bacilli became less numerous and the spirochetes predominated (Fig 10). The latter increased in numbers from the margin to the bronchopneumonic areas for a short distance and then disappeared. Cocci were seen in remote areas of consolidation, often forming clumps in the alveoli.

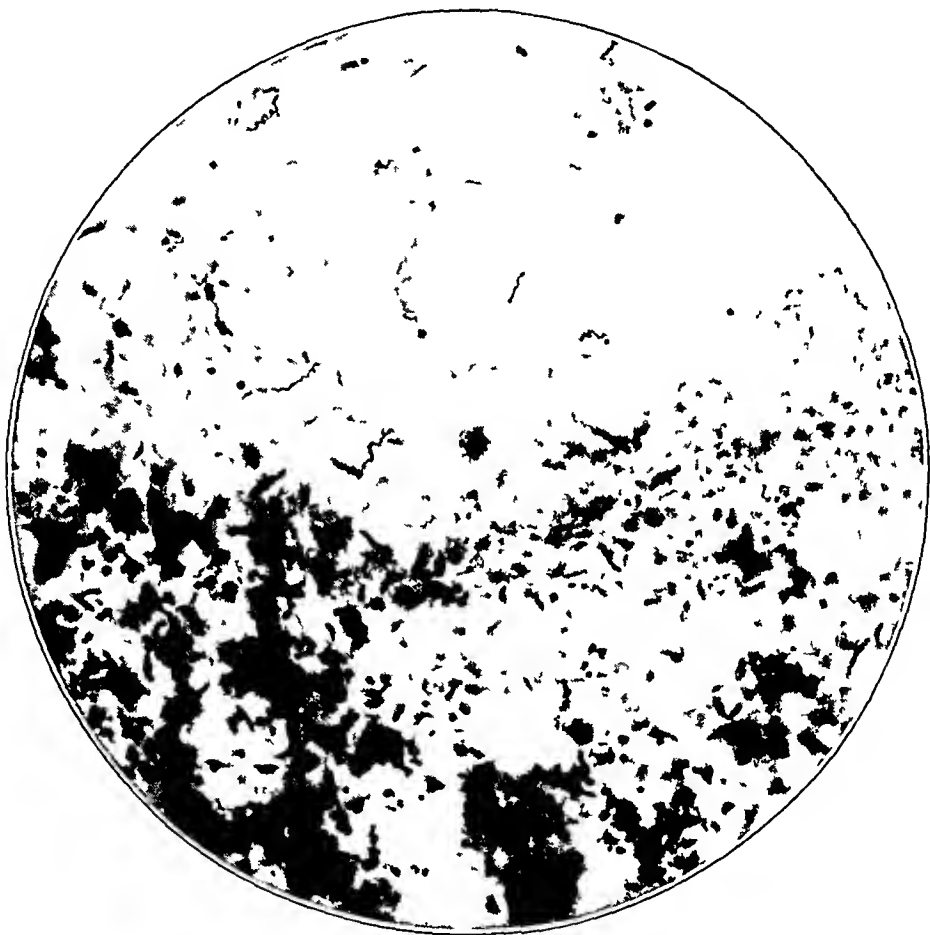


Fig 10 (Case 19) —Margin of abscess cavity in pulmonary gangrene revealing spirochetes migrating into less involved tissue while numerous fusiform bacilli and cocci occur in the necrotic areas (Levaditi stain)

A rare type of complication was the occurrence of gangrene in a pulmonary infarct in a patient with chronic cardiac decompensation.

CASE 20—J W, a man, aged 57. The anatomic diagnosis was as follows:

Intrapulmonary thrombosis of branches of pulmonary arteries, infarction of right lung with gangrene, chronic mitral and aortic endocarditis, passive congestion of the liver with brown induration, ascites, edema of the penis, scrotum and legs, slight icterus.

The right lung near the center of the anterior surface presented an area of 10 cm in diameter, from dark green to black in color with a soft center. On section of this area a cavity was encountered, filled with foul, black material.



The walls were soft and greenish black. In one of the vessels leading to this region of the lung a thrombus was found. The remainder of the lung contained a few scattered, slightly nodular areas of bronchopneumonia.

Smears of the necrotic material revealed many streptococci, various forms of fusiform bacilli, but no spirochetes.

Of special interest was the occurrence of fusospirochete infection engrafted on carcinoma of the lung.

CASE 21—A P, the anatomic diagnosis of whom was as follows. Primary bronchogenic carcinoma of the right upper lobe with metastasis in the mediastinal glands, bronchiectasis of the entire right lung, bronchopneumonia of upper and lower lobes with multiple foci of gangrene. Pressure on the vena cava, edema of the tissues of the head, neck, upper thorax and extremities, marked pyorrhea alveolaris.

Smears from necrotic areas revealed many cocci, short gram-negative bacilli (*B. influenzae*) and fusiform bacilli.

In microscopic sections there appeared confluent bronchopneumonic areas, with marked interstitial tissue infiltration. Areas of necrosis contained large masses of bacteria and debris. The alveoli were filled with fibrin, serum and polymorphonuclear leukocytes. The interstitial tissue was infiltrated with polymorphonuclear leukocytes. Large vessels contained thrombi, made up of fibrin, pus cells and bacteria (cocci and bacilli). Mucosa of the small bronchi was necrotic on the surface and densely infiltrated with cells in the deeper portions.

In the Levaditi sections many forms of fusiform bacilli, short, long and thread-like, together with cocci but no spirochetes could be demonstrated.

CASE 22—P, a man, complained of cough, foul expectoration, rapid loss of weight over a period of several weeks. The sputum was foul, formed three layers and contained many fusiform bacilli, cocci and a few spirochetes. In cultures *Streptococcus viridans* was obtained.

At necropsy, the right lung revealed bronchogenic carcinoma with multiple putrid abscesses. Similar organisms were observed in the abscess cavities, as in the sputum.

The association of fusospirochete infection with pulmonary tuberculosis, while rare, was encountered in five patients. The lesions complicating the tuberculosis were bronchiectasis, abscess and gangrene, and were described recently.<sup>9</sup>

The complications were observed in five patients. In the first, marked fetid expectoration was accompanied by far advanced pulmonary tuberculosis.

CASE 23—A woman, aged 25, colored, developed foul expectoration for the last few months in the course of tuberculosis of five years' standing. She was greatly emaciated and presented typical signs of cavities in left upper and right lower lobes. The sputum was intensely foul, of green color, and revealed numerous tubercle bacilli, in addition to large numbers of fusiform bacilli, spirochetes and cocci. Necropsy was refused. A clinical diagnosis of pulmonary gangrene superimposed in a far advanced ulcerative tuberculosis was made.

CASE 24—F M, a man, white, aged 38, developed cough and foul expectoration two months prior to entrance to hospital. He was apparently in good health up to that time. The sputum was foul and green and contained tubercle bacilli, fusiform bacilli, cocci and very few spirochetes. The patient was given 0.9 gm neo-arsphenamin but he was already desperately ill and died seven days after entrance. At necropsy there was a diffuse gangrene of the right lung and a chronic fibrocaceous tuberculosis of both upper lobes. Of special interest was the enormous numbers of spirochetes found in the lung, although

<sup>9</sup> Pilot, I, Davis, D J, and Shapiro, I F. Am Rev Tuberc 8 249-259, 1923.

the sputum revealed only a few (Fig 11) The fusiform bacilli and cocci, which were abundant in the sputum, occurred in the bacterial masses lining the gangrenous cavity, while spirochetes were numerous at the margin and away from the abscess wall An emulsion of the gangrenous area injected experimentally into rabbits produced putrid lesions

Fusospirochete infection was noted in three tuberculous patients with bronchiectasis

CASE 25—A youth, aged 13, colored, developed cough, pain in chest and a fetid sputum following tonsillectomy The sputum contained bacilli, spirochetes and cocci, but no tubercle bacilli were demonstrated At necropsy the anatomic diagnosis was Multiple putrid bronchiectatic cavities of both lungs, multiple putrid abscesses of the right lung, a right sided putrid empyema, miliary tuberculosis of all lobes, caseous tuberculosis of the peribronchial lymph glands

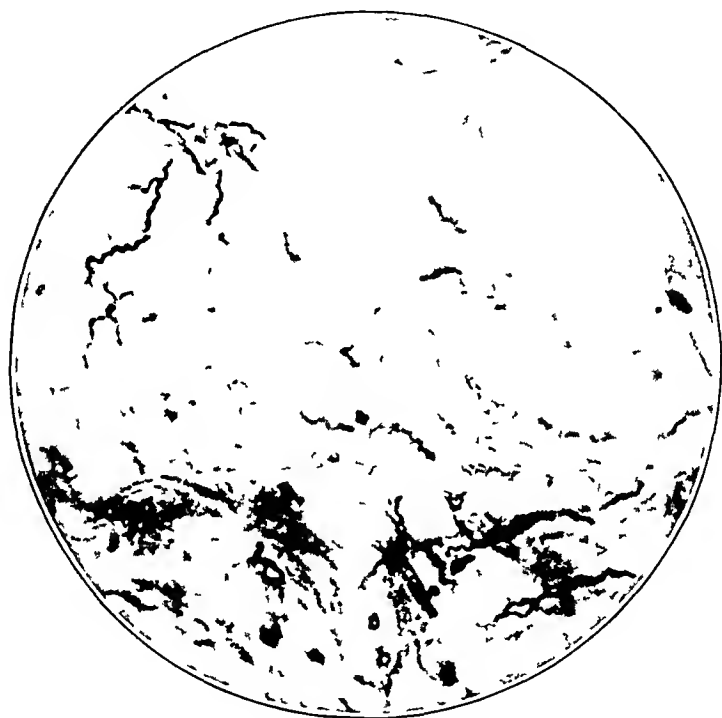


Fig 11 (Case 24)—Spirochetes in tuberculous lung (Levaditi stain)

CASE 26—A man, aged 45, white, had a cough and profuse expectoration for three years A fetid odor was noticed at intervals While under observation he had a temperature of from 103 to 104 with foul breath, fetid expectoration, and on physical and roentgen-ray examination many small bronchiectatic cavities in the right lung The sputum formed three layers, and contained many fusiform bacilli, spirochetes, cocci and a moderate number of tubercle bacilli

CASE 27—A man, aged 34, gave a history of cough and foul expectoration for two years Physical and roentgen-ray examination presented dense infiltration of both upper lobes with a small cavity formation The sputum formed three layers and contained fusiform bacilli, spirochetes, streptococci and tubercle bacilli

Previous infection in the respiratory tract predisposes to fusospirochete infection The incidence of such complication in bronchitis and

lobar pneumonia is surprisingly low. Indeed, it is often difficult to ascertain if the pulmonary abscess is definitely preceded or is associated with these conditions.

CASE 28—M. P., a woman, aged 38, entered hospital Aug. 29, 1921, with clinical evidences of lobar consolidation of the left upper lobe. Resolution was delayed and it was thought that tuberculosis may have been the complicating factor. However, repeated sputum examinations for tubercle bacilli were negative. Physical findings became fewer, accompanied by the general improvement of the patient who was sent home. She remained without symptoms until one year later when she began to cough and expectorate profuse quantities of sputum which was often blood-tinged and foul. The temperature was 103.2, pulse 126, respiration 40. The breath was foul, the chest revealed dullness over the right lower lobe, impaired resonance over both upper lobes with amphoric breathing in the upper left lobe anteriorly. Moist râles were heard over the right lower lobe in the axillary region, and over the left upper lobe anteriorly. The sputum was extremely foul, of large quantity, green, and in smears contained cocci, fusiform bacilli and a few spirochetes. The cultures aerobically showed *Streptococcus viridans*, *B. capsulatus* and anaerobically *B. fusiformis*. The blood picture was that of secondary anemia, with 60 per cent hemoglobin, 3,160,000 erythrocytes, and 10,400 leukocytes. A diagnosis of multiple abscesses was made. She was given sodium cacodylate, two and a half grams daily, subcutaneously. Improvement was gradual with a fall in temperature to 100, less expectoration and fewer râles in the chest. After six weeks the sputum was still of considerable quantity but not foul. Leukocyte count at this time was 7,400. In the following four weeks the temperature became normal and the sputum less profuse. Physical and roentgen-ray findings of cavitations near the hilum of the left lung were still present when the patient was discharged.

CASE 29—I. K., a man, aged 30, entered with a history of cough, foul smelling sputum and pain in the right chest for three months. Apparently shortly before the onset of foul expectoration he had suddenly developed a chill with pain in the chest and cough, a clinical picture like that of lobar pneumonia.

Examination disclosed a well nourished man, with very foul breath. Carious teeth and marked pyorrhea were striking. In the chest, dullness occurred over the right lower lobe with crepitant and large moist râles in the right lower and middle lobes. Sputum contained fusiform bacilli, and cocci but no spirochetes or tubercle bacilli. The temperature varied from 101 to 104, the pulse from 100 to 120, respiration from 36 to 40. The blood examination gave 75 per cent hemoglobin, 3,400,000 erythrocytes and 13,400 leukocytes. The Wassermann test was negative. In the roentgen-ray film a dense shadow involved the lower half of the right upper lobe, merging gradually into more normal tissue. The right pleural cavity had a fluid level. The patient rapidly became worse as the pleural cavity filled.

The anatomic diagnosis at necropsy was as follows:

Putrid abscess of the right lower lobe with rupture and right pyothorax resolving pneumonia of the right lower lobe, lobar pneumonia of the right middle and upper lobes, right fibrous and fibrinous pleuritis, hypostatic bronchopneumonia of the left lower lobe, fibrinous pleuritis of the left pleura, acute hyperplasia of the tracheobronchial lymph glands, latent tuberculosis of peribronchial lymph glands, cloudy swelling of parenchymatous organs, pyorrhea alveolaris.

On removal of the right lung, a large abscess cavity containing thick, foul, creamy pus was opened. The cavity was situated in the posterior lateral surface of the right lower and middle lobes, measuring 24 cm long by 17 cm wide and deep and communicating with the pleural cavity which contained similar

pus The visceral pleura was covered with fibrinous exudate The cut surface of the upper and middle lobes were consolidated except for apex and anterior margin

Smears of the pus revealed cocci, fusiform bacilli and a few spirochetes In aerobic cultures *Streptococcus hemolyticus* predominated and a few pneumococci appeared, anaerobically, pleomorphic forms of fusiform bacilli occurred

In microscopic section of the abscess region the picture was that of interstitial bronchopneumonia extending from the necrotic abscess wall The alveoli were filled with polymorphonuclear leukocytes, fibrin, bacteria and epithelium The interstitial tissue was infiltrated with round cells, largely lymphocytes The bronchi were lined by granulation tissue and contained masses of bacteria free in the lumen The blood vessels showed moderate endarteritis In Levaditi preparations the pyogenic wall was made up of enormous masses of bacteria, consisting of a mixture of bacilli, cocci and spirochetes The spirochetes showed no migrating tendency Cocci, however, were found in the more remote consolidated areas

*Comment*—The course appears to have been first pneumonia, later a local gangrene in the involved lobe with terminal lobar and lobular consolidation in the other lobes

CASE 30—J D, a man, aged 52, a butcher, entered with a history of cough, pain in right chest and fever for ten days The cough was at first nonproductive Later, slightly purulent sputum was expectorated

During the first week of observation, the temperature remained at 102 or 103 F, the pulse from 86 to 100 Blood examination gave 21,300 leukocytes, 85 per cent hemoglobin Expectoration increased and was noted to be distinctly foul The sputum was blood tinged and formed three layers Smears revealed 90 per cent polymorphonuclear leukocytes, cocci, fusiform bacilli, spirochetes and diphtheroids In cultures the cocci appeared predominantly *Streptococcus viridans* with a few colonies of *Streptococcus hemolyticus* Roentgen-ray plates showed clouding of the central portion of the right lower lobe, extending from the fourth costochondral junction to the fifth interspace anterior and from the hilum shadow to the periphery of the chest The upper margin of shadow was rather definitely outlined The lower margin was lost in a diffuse haziness, then gradually faded out toward the dome of diaphragm In the center of the shadow there was a circumscribed area of decreased density, about 2 cm in diameter, and just medial to that two more similar areas 1 cm in diameter No fluid level was demonstrable The left lung was clear

The patient was immediately placed on neo-arsphenamin therapy Improvement was rapid Roentgen-ray plates in seven days showed a diminution in the extent of findings Density was smaller and cavitations less distinct The temperature and pulse at this time were normal The cough and expectoration ceased Four weeks later the shadow had almost completely disappeared, and aside from thickening of the pleura no abnormal physical findings could be elicited

In three patients trauma may have played a role as a predisposing factor The injuries may, however, have been coincident The history, as given by the patient, would seem to indicate that fusospirochete infection may follow an injury, particularly to the chest

CASE 31—C M, a man, aged 50, white, complained of cough, pain in the chest and weakness for two months He attributed his symptoms to the result of an injury by an iron door that fell on his back A cough started one week later Three weeks later foul expectoration appeared Physical examination disclosed a fairly well-nourished man, with very foul breath Several teeth were carious, tartar deposits heavy, and there was pyorrhea of moderate severity The chest revealed dulness over the left lower lobe posteriorly, with crepitant râles in this region and in the right axilla There was slight edema of the ankles Blood pressure was 110 systolic and 80 diastolic The tempera-

ture varied from 98 to 101, with elevation in the afternoon, the pulse from 80 to 100. The urine was normal. The blood count showed 56 per cent hemoglobin, 3,968,000 erythrocytes, 14,700 leukocytes, differential count of 70 per cent polymorphonuclears, 22 small lymphocytes and 8 large mononuclear leukocytes. The sputum averaged 12 ounces (355 cm) daily, forming three layers of grayish green color, was of foul odor and contained many elastic fibers. Smears of teeth and surface of tonsils showed many bacilli, spirochetes and diplococci. Repeated examinations of the sputum were negative for tubercle bacilli and spirochetes. Large numbers of fusiform bacilli, however, were



Fig 12 (Case 31) —Multiple abscesses of lung

present. In cultures, *Streptococcus viridans* was predominant, associated with a few colonies of hemolytic staphylococci and micrococcus catarrhalis. Roentgen-ray film demonstrated irregular cavities in the lower portion of the left lung (Fig 12). The right lung was emphysematous. A diagnosis of multiple abscesses was made.

Neo-arsphenamin (0.9 gm) was administered once a week for seven weeks. Improvement was distinct. Expectoration was less foul and the temperature was lower (from 98 to 99). An artificial pneumothorax was then performed and repeated in one month. The sputum diminished in amount, was only slightly foul and in smears revealed fewer fusiform bacilli. Two months later

expectoration was only slight and had no odor. Roentgen-ray film showed a partially collapsed lung. The patient left the hospital and did not return for further observation.

CASE 32—A man, aged 32, colored, complained of sharp pain in the left chest, cough and shortness of breath for a period of one month. Previous to onset of the cough he had noticed loss of strength and had a tired feeling. He had a sudden paroxysm of coughing one evening, which lasted for fifteen minutes. Expectoration did not begin until two weeks later. In the past history, it was noted that he had been shot in the chest. He did not recall the pulmonary symptoms following the shooting. Three years later he had a definite hemoptysis. Physical examination revealed dulness and a few inconstant râles over the right apex. Flatness and decreased breath sounds were elicited over the right lower lobe.

The temperature varied from 100 to 103, the pulse from 90 to 130, respirations from 24 to 38, leukocyte count was 11,300. The sputum was green, liquid, very foul and contained many fusiform bacilli, spirochetes and cocci. Smears from the teeth showed an abundance of the same organisms.

Roentgen-ray film demonstrated the fluid level of a pyopneumothorax up to the second costal cartilage on right side with displacement of the heart to the left. The pus aspirated from the pleural cavity was very foul, green, and in smears showed large numbers of bacilli, spirochetes and cocci. Aerobic cultures gave no growth. Anaerobic blood agar cultures gave *Streptococcus viridans* and fusiform bacilli. Cultures of sputum showed similar organisms.

The patient died three days after admittance. Necropsy was refused.

CASE 33—M. S., a woman, aged 37, white, complained of cough, foul odor to breath, and expectoration of large quantities of foul sputum. Two years previously she had fallen on ice breaking her right forearm, but apparently had had no direct injury to the chest. Four months later she became ill with pain in the chest, followed by cough and foul expectoration within four weeks. Lung abscess was the diagnosis at that time and some relief followed a direct aspiration. On physical examination the patient appeared fairly well-nourished. Several teeth were carious, some pyorrhea was noted. The chest presented dulness and moist râles over the right lower lobe. In the roentgenogram the apices were clear and the right hilum shadow increased. In the right lower lobe a shadow was evident, 8 by 10 cm. in size, extending to the level of the third rib anterior and fifth rib posteriorly containing small abscess cavities. The temperature varied from 99 to 100, the pulse from 80 to 110. The blood count presented 75 per cent hemoglobin, 4,070,000 erythrocytes, 9,450 leukocytes, differential count of 88 per cent polymorphonuclears, 7 per cent large lymphocytes, 4 per cent transitionals and 1 per cent eosinophils. The sputum was of green color and liquid, containing a small piece of gangrenous lung tissue. Smears from this portion revealed large numbers of spirochetes, fusiform bacilli and cocci in large masses. The aerobic cultures contained *Streptococcus viridans* and the anaerobic, streptococci and typical fusiform bacilli.

Surgical drainage was attempted, but death ensued twenty-four hours later. No necropsy could be obtained.

The development of fusospirochete infection in the lung without any well-defined predisposing factors is of special interest. In some patients perhaps, bronchitis existed without any definite knowledge of this on the part of the patient, or an upper respiratory infection not severe enough to impress the patient. On the other hand, the anaerobes and associated pyogens may have attained an added virulence under certain conditions sufficient to invade the apparently normal lung. It is

also possible that these organisms may cause lesions in persons whose general resistance has been greatly lowered. The two fatal cases were in colored persons who appeared to have low resistance. The first patient in whom we observed gangrene due to these organisms did not give any history or evidence of predisposing factors.



Fig 13 (Case 34) —Early stage of pulmonary gangrene

CASE 34—G C, a man, aged 32, colored, complained of cough and blood-tinged expectoration, pain in the chest and loss of weight, which had developed gradually five months previously. No history of bronchitis, pneumonia or anesthesia could be obtained. Physical examination presented a fairly well nourished man. Several teeth were carious and some pyorrhea alveolaris was present. The breath was extremely foul. The chest revealed impaired resonance of the right upper lobe, bronchovesicular breathing and crackling râles over this region. The sputum was blood streaked, of foul odor and contained numerous fusiform bacilli and spirochetes, and gave gram-positive cocci but no tubercle bacilli. The blood count was 7,200 leukocytes and 4,520,000 erythrocytes. In an examination two weeks later, it was noted that the râles were

more numerous, extending over the entire right upper lobe and the upper part of the lower lobe. Roentgen-ray film showed a solid shadow extending to the hilum involving the same parts of the right lung (Fig 13). One week later the films revealed a circular shadow in the right upper lobe about 5 cm across, extending almost to the periphery. The temperature at this time was 100, pulse 84, respiration 24.

An attempt was then made to drain the abscess cavity through a rib resection. Two cubic centimeters of blood-tinged foul smelling pus was aspirated from the right upper lobe. Smears showed gram-positive diplococci, fusiform bacilli and spirochetes (Fig 14). Aerobic cultures were sterile, while in the anaerobic cultures many colonies of *Streptococcus viridans* and fusiform bacilli were obtained.

Expectoration continued to be profuse and of foul odor (Fig 15). The pus from the chest wound was of the same character. For a period of three weeks

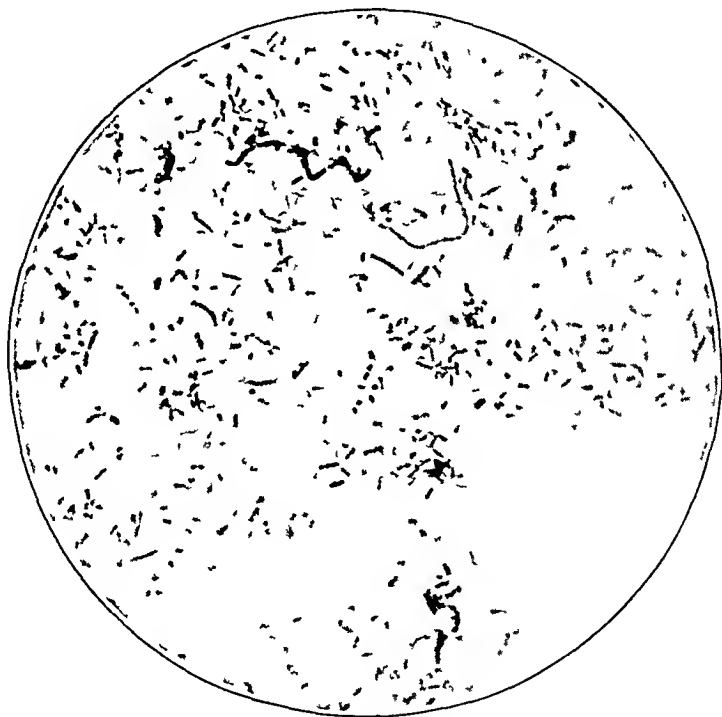


Fig 14 (Case 34) —Smear of putrid pus aspirated from pulmonary abscess, revealing fusiform bacilli, spirochetes, and streptococci (carbolfuchsin stain)

the patient appeared to expectorate and drain less, and his general condition improved, with a normal temperature and pulse. He quickly developed signs of empyema, and from the right pleural cavity 1,600 cc of very foul pus was aspirated. The aerobic cultures of this pus were sterile. The patient died eight hours later.

The anatomic diagnosis at necropsy was

Multiple gangrenous abscesses of the right lung, involving the upper and greater part of the lower lobe, putrid empyema (1,000 cc of pus) of the right pleural cavity, acute hyperplasia of the mediastinal lymph glands, emphysema of the left lung, left sided serofibrinous pleuritis (30 cc of turbid fluid).

Smears of pus from the abscess and from the right pleural cavity revealed gram-positive cocci, fusiform bacilli and spirochetes but no tubercle bacilli. In cultures *Streptococcus hemolyticus*, *Staphylococcus aureus* and fusiform bacilli aerobically were obtained.



Microscopic section presented confluent areas of interstitial pneumonia with foci of gangrene. In the abscess wall a mixture of fusiform bacilli, cocci and spirochetes appeared, while spirochetes were found in great numbers at the margin of the abscess.

In Case 35, the genito-urinary condition may have profoundly lowered the general resistance.

CASE 35—S. D., a man, aged 34, colored, entered the hospital extremely ill, with a history of cough, pain in the chest for nine days, associated with headache, abdominal discomfort and vomiting.



Fig 15 (Case 34) —Later stage of pulmonary gangrene after attempted surgical drainage

Examination revealed a well-developed, delirious man. The lips were covered with herpes. The teeth had heavy brown deposits. The chest presented scattered areas of bronchovesicular breathing and moist râles over both lower lobes. A urethral discharge containing gram-negative diplococci was present. The temperature was 103.4, pulse 124, respiration 48, the blood showed 70 per cent hemoglobin, 3,280,000 erythrocytes and 8,400 leukocytes, the culture was sterile. The patient died forty-eight hours after entrance, and at necropsy the anatomic diagnosis was as follows:

Multiple abscesses of both lungs, acute hyperplasia and edema of the tracheo-bronchial lymph glands, latent tuberculosis of the apex of the right lung, cloudy swelling of the liver and spleen, bilateral acute cysto-ureteropyelo-

nephritis, fibrous urethral stricture at the proximal end of anterior urethra with urinary extravasation, periurethral necrosis, hypertrophy and coarse trabeculations of urinary bladder

The left lung contained numerous scattered button like nodules, which on section were dark red, raised areas with soft necrotic centers. The right lung contained similar nodules, from 2 to 6 mm in diameter

In smears made from the necrotic centers, fusiform bacilli, cocci, spirochetes and short gram-negative bacilli were demonstrated. Cultures contained *Streptococcus hemolyticus*, *B. capsulatus* and pleomorphic forms of *B. fusiformis*

Sections showed confluent areas of bronchopneumonia with foci of necrosis. The alveoli contained serum, pus cells and desquamated epithelium. In the necrotic areas enormous numbers of cells and bacteria were found. The masses of bacteria formed structures similar to actinomyces granules but no true actinomyces were demonstrable. In Levaditi sections the actinomyces-like structures revealed a mixture of typical and thread forms of fusiform bacilli, short bacilli (*B. capsulatus*), cocci and spirochetes of various types. At the margin, chiefly spirochetes and a few short bacilli were found. In the adjoining consolidated areas the alveoli contained leukocytes and short bacilli resembling morphologically *B. capsulatus*

In two other patients with lung abscess neo-arsphenamin was employed with favorable results

CASE 36—J. R., a man, aged 53, white, complained of stench from mouth, cough, foul expectoration and pain in chest. The onset was gradual seven weeks previously with apparently no determining cause. He had had a nasal operation under local anesthesia three years prior to the present trouble. There were no complications

Physical examination disclosed a well nourished, robust person. There were several carious teeth and marked pyorrhea. The tonsils were enlarged and slightly congested. The breath was very foul. The chest presented moderate emphysema and no dulness or rales were demonstrable. The fingers were clubbed. The temperature varied from 97 to 101, the pulse from 72 to 90. The urine contained a trace of albumin. The blood showed 60 per cent hemoglobin, 3,670,000 erythrocytes, 17,600 leukocytes, with a differential count of 54 per cent polymorphonuclear leukocytes, 20 per cent small lymphocytes, 10 per cent large mononuclears, 6 per cent eosinophils, 4 per cent, basophils, and 6 per cent transitional leukocytes. The Wassermann reaction was negative

The sputum was foul and formed three layers. In smears many spirochetes, fusiform bacilli and cocci appeared. Aerobic culture contained equal numbers of *Streptococcus viridans* and *Streptococcus hemolyticus*, anaerobic, pleomorphic forms of fusiform bacilli

The roentgen-ray film presented a density in the deep portion of the right lower lobe, with a small cavity containing a distinct fluid level. Neo-arsphenamin (0.6 gm) was administered. The sputum diminished in amount. The dose was repeated. The sputum remained foul and still contained bacilli and spirochetes. Roentgen-ray film, however, showed less cloudiness and no cavity or fluid level. Two weeks later, the expectoration was slight, temperature normal, and roentgenogram revealed still less cloudiness. The patient left the hospital and did not return for observation

CASE 37—J. A., a man, aged 29, white, entered with a history of persistent cough, expectoration of foul, blood-tinged sputum, and sharp pains in the right chest. These symptoms came on gradually, following what the patient considered a mild cold six weeks previously. On examination, he appeared well nourished. The breath was foul and the teeth carious. The chest presented dulness, increased tactile fremitus, tubular breathing and coarse râles over the right lower lobe. The temperature was 99, pulse 90. Leukocyte count was 18,100 with 75 per cent polymorphonuclear leukocytes. The sputum was foul. Smear showed numerous fusiform bacilli, cocci and a few spirochetes. Tubercle bacilli

were not found. In the roentgenogram the apexes were clear, the right cardio-diaphragmatic angle obscured by an irregular density in the right lower lobe. No cavity was demonstrable. Two doses of 0.45 gm of neo-arsphenamin and two of 0.6 gm were administered at intervals of from four to six days. Expectoration became less, the breath and sputum lost their foul odor, the cough diminished and the temperature became normal. Roentgen-ray examination revealed great reduction in the density, while the physical signs greatly diminished.

#### BACTERIOLOGY

The bacteriologic studies were made of the sputum and the tissues at necropsy by smears and cultures. Aerobic cultures were obtained on 10 per cent blood agar plates by streaking the washed sputum or pus on the surface, and by the poured plate method. Anaerobic cultures were made on blood agar slants by the Wright method. In sections, the bacteria were stained by the Weigert and Levaditi technic.

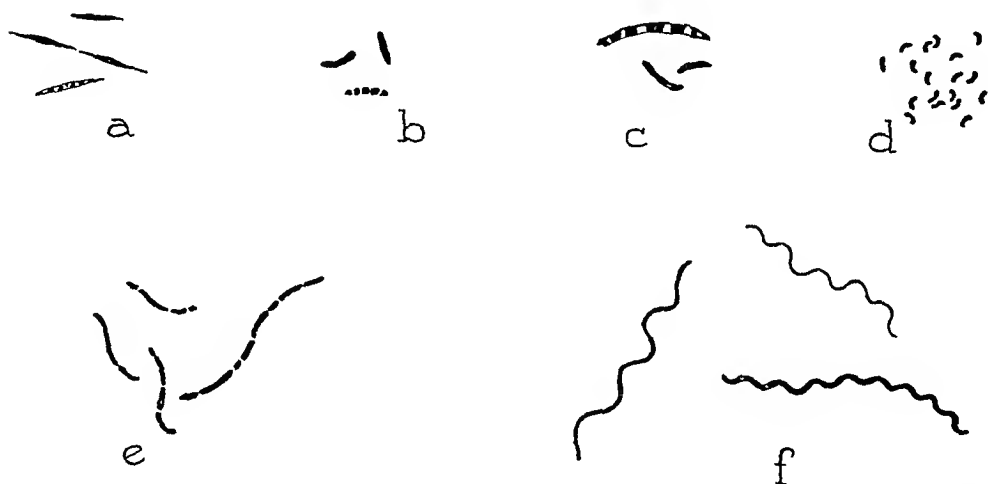


Fig 16—Types of fusiform bacilli and spirochetes observed in putrid lesions of the lungs. Similar forms are observed about teeth and tonsils. Typical fusiform, solid and granular (a), curved fusiform solid and barred (b and c), short forms or comma bacilli (d), pleomorphic forms seen in cultures (e), fine and coarse spirochetes.

The organisms found in the lesions conform, for the most part, in their morphology and cultural characteristics to those describing the teeth and tonsils. The fusiform bacilli appear as typical forms, often barred and slightly curved. Thread like, mycelial like organisms may be pleomorphic forms. The latter never branch, and about them many of the typical bacilli and spirochetes may be grouped. Short fusiform bodies or comma bacilli often are associated. They are gram-negative and non motile (Fig 16). The spirochetes are actively motile, gram-negative, fine or coarse, forming from four to ten turns, resembling in morphology the forms called *Spirochaeta vincenti*, *Spirochaeta macrodentium* and *microdentium* (Fig 16). The cocci invariably associated with anaerobes are gram-positive diplococci, which on culture are most

often *Streptococcus viridans*, occasionally *Streptococcus hemolyticus* and in some instances both. The viridans type may show anerobic properties. In their fermentative properties and pathogenicity for rabbits, these streptococci correspond to those observed about teeth and tonsils. In the majority of instances the before mentioned organisms occur in symbiosis, but in a few either staphylococci, influenza bacilli, leptothrix, *B. capsulatus*, and *Micrococcus catarrhalis* may be found. In fatal cases the *Streptococcus hemolyticus* is most constantly associated with the anerobes.

The mode of infection with these organisms is readily understood where aspiration is a factor. Following general anesthesia, tonsillectomy, perforating lesions, the secretions of the mouth rapidly give rise to pathologic changes in the lung. In the tuberculous lung, or in bronchiectasis the organisms may secure a foothold probably by inhalation of droplets carrying these organisms, first as saprophytes, later producing lesions varying from putrid bronchitis to gangrene. It is possible that in a few instances these bacteria may enter as emboli from a focus and form a metastatic lesion in the lung. Where the spirochetes are found in the lung, such is probably not the route, as in the blood stream the spirochetes apparently are destroyed. In rabbits injected intravenously with mixtures, the spirochetes disappeared while fusiform bacilli and cocci are demonstrable in the pulmonary lesion. Similar findings are encountered in the metastatic putrid brain diseases complicating putrid bronchiectasis.

In the instances where these organisms cause lesions in the normal lung, or at least in a lung where no local predisposing factor is demonstrable, the organisms concerned may be of enhanced virulence or possibly of exogenous origin. Epidemics of Vincent's angina and noma have been described<sup>9</sup> where such exogenous bacteria are responsible. While as yet we have made no observations indicating epidemic fusospirochete pulmonary infection, such epidemic strains may appear in an outbreak of pulmonary infections.

#### PATHOLOGY

The lesions observed due to these organisms are of a great variety, depending to large extent on the underlying factors, the resistance of the patient, and the behavior of the pathologic process. In all, the tendency to necrosis and the production of a foul smelling lesion are the striking characteristics.

The simplest lesion occurs in the form of a putrid bronchitis. Buday observed such cases at necropsy, in which the necrosis was limited to the mucous membrane, and the lumen was filled with masses of

bacteria and detritus. We have observed similar lesions in the bronchi but associated in all instances with a necrotic process in the lung parenchyma.

A more commonly seen lesion is that of a bronchopneumonic consolidation in any lobe, with formation of a single abscess cavity. In this type the bronchopneumonia surrounding the abscess cavity appears as an interstitial form with intense cellular infiltration at abscess wall. The cavity is covered with shaggy green membrane of fibrin and masses of bacteria. Fusiform bacilli and cocci may form the center of the clumps, while at the periphery the comma bacilli and spirochetes may be abundant. In the membrane the bacilli and cocci appear predominantly, the spirochetes, however, are most numerous at the margin. The cocci extend up through the lymphatics in the alveoli walls and septa. In the more extensive lesions, the bronchopneumonic areas may be confluent, and the areas of necrosis and cavity formation multiple. Occasionally, discrete or lobular forms of bronchopneumonia with central softening is seen (Fig 3). The distribution of the bacteria resembles that seen in the solitary abscess, but the spirochetes begin to show a tendency to migrate away from the margin of the necrotic wall. The lesions are more gangrenous in character, with green discoloration of the involved areas. These lesions may be seen at necropsy in all stages, acute, subacute, and chronic forms with considerable fibrosis and thickening of the bronchi.

Of great interest is the diffuse form of gangrene. This lesion represents the result of the action of the anaerobes at their highest pathogenic power. A whole lobe or the entire lung may be involved with multiple cavitations, some of which may become a huge size. The entire lung is discolored green and is very putrid. In the cavities, large sloughs of tissue and fibrin occur. The bronchi and pleura are invariably involved. Microscopically, the consolidation is in the formation of an interstitial pneumonia (Fig 5). The infiltrating cells are predominantly of the mononuclear types. In the region close to the cavity, the alveoli are filled with fibrin and large numbers of mononuclear cells. At the margin and in the necrotic tissue masses of enormous numbers of bacteria and degenerated polymorphonuclear leukocytes are seen. The spirochetes at the margin appear innumerable, and are seen migrating in great numbers into the neighboring tissue (Figs 4 and 1 a). Cocci are found in the lymphatics and alveoli of the most remote portions.

The blood vessels in the more extensive processes are filled with thrombi, which may be rich in bacteria clumps, made up of fusiform bacilli, spirochetes and cocci. Such thrombi are probably the source of the metastatic lesions in the brain. The bronchi are often filled with necrotic tissue and bacteria. The mucosa may be ulcerated and the

bacteria may be seen extending under the mucosa into the alveoli. The peribronchial lymph glands become enlarged and soft but not necrotic. The pleura frequently is covered with fibrin. Old cases show many fibrous adhesions. The pleural cavity often is typically involved with the formation of a serofibrinous exudate containing streptococci. In the diffuse types of gangrene, a cavity may rupture through the pleura with the production of foul, green pus, containing similar forms of bacteria as in the lung. The pericardium may be involved in a terminal sero-fibrinous pericarditis.

The other portions of the lung, aside from the gangrenous areas, may be the site of a nongangrenous bronchopneumonia, edema and marked congestion. Tuberculosis of various forms, bronchiectasis (Fig 7), and carcinoma may be associated as underlying factors. The parenchymatous organs show cloudy swelling in the more acute cases. Of special interest is the occurrence of brain abscess, particularly with putrid bronchiectasis (Fig 8). The lesion is usually in the parietal lobe. The abscess wall is shaggy and necrotic and reveals fusiform bacilli and cocci but no spirochetes (Fig 9). The streptococci may extend along the pia into the meninges and give rise to acute meningitis.

It would seem that the streptococcus or other pyogens affect the tissue first, preparing the soil for the growth of the anerobes. The putrid portions correspond to the distribution of the bacilli and spirochetes. The latter advance before the bacilli and may be found in areas of little or no necrosis. The pyogens spread through the lymphatics into the connective tissue, causing interstitial pneumonia in remote portions and serofibrinous pleuritis.

#### SYMPTOMS

The symptoms are variable, depending on the type of lesion. Acute and chronic forms of fusospirochete infection are to be considered. The foul expectoration, in which the causative organisms are demonstrable, is common to both. Physical signs will depend on the location of the lesion. The course and termination are very inconstant.

#### ACUTE

Both abscess and gangrene may develop rapidly, particularly after some definite etiologic factor, such as anesthesia or perforation of the bronchi. In the simple abscess, cough sets in, first nonproductive, together with rise in temperature and usually leukocytosis. The lesion softens in from twelve to fourteen days and may drain gradually or rupture suddenly into a bronchus, with the expectoration of foul smelling pus. Physical signs are variable and may be wanting or are sometimes obscured by a moderate effusion on the affected side. The

roentgen ray is of value at this period. A solid shadow with cavity formation, often with fluid level, develops. As the lesion resolves, physical signs become fewer, the cavity smaller, and the density disappears in the roentgen-ray film. Most of the single abscesses terminate favorably, with drop of temperature to normal in from a few days to several weeks, disappearance of expectoration and physical signs of consolidation. In a few, progressive involvement of new areas with the formation of new cavities may occur. After a period free from symptoms, fever and foul expectoration may recur and evidences of consolidation reappear.

The formation of multiple cavities leads to a more severe form and prolonged course of the disease. A septic type of temperature, progressive loss of weight, increasing rapidity of pulse, profuse expectoration of foul sputum may be extended over a period of several weeks or months. In some, only a slight temperature rise with varying amounts of expectoration may be periodic. The physical signs are most extensive, involving most often the lower lobes.

Acute gangrene usually appears with fever, pain in the chest and cough with the development later of very foul breath and putrid liquid green expectoration. The physical findings may show involvement of an entire lobe or lung, with signs usually of large cavitation in the diffuse form of gangrene. The roentgen ray presents diffuse infiltration with cavities and rapid progressive involvement of new areas. The course is generally over a period of two or more weeks, with death from the overwhelming toxemia. In the lobular or bronchopneumonic type of gangrene, the clinical picture is not so severe or progressive, and it develops as a rule into a chronic state which may persist for months. During this stage, periods of improvement, of no fever or of slight expectoration may often alternate with periods of pyrexia, toxemia and foul expectoration.

In bronchiectasis, the ordinary symptoms extend over a period of many years. At various intervals the patient may complain of the foul smelling expectoration and constitutional symptoms. When such symptoms arise, it is often the result of superimposed infection or an extension into the uninvolved tissues by fusiform bacilli, spirochetes, and associated pyogens. Fever of from 100 to 102, foul breath, leukocytosis, from 9,000 to 15,000, usually develop at this time. The sputum may be greatly increased in quantity and is decidedly more putrid and often blood stained. The organisms appear in great numbers. When improvement begins, the odor diminishes and the numbers of bacteria become fewer. One can, however, demonstrate the anaerobes in moderate numbers in sputum with no odor. It would appear that the odor results from poor drainage of the cavities and from the necrosis in the walls of the cavities and adjacent tissues. Physical signs are

more diffuse during febrile periods and new cavities may become demonstrable in the more extensive lesions. The roentgen ray is of particular value, revealing fresh infiltrations about the older bronchiectatic cavities, with bronchopneumonic areas in more remote parts which in the more serious infections may become confluent and form new cavitations.

#### COMPLICATIONS

Extension of infection to the pleura is not uncommon in abscess, gangrene or bronchiectasis. Serofibrinous pleuritis may develop with an effusion which obscures the physical and roentgen-ray signs of lung involvement. In most instances the exudate contains streptococci and has no odor. A more serious complication is the development of putrid empyema or pyopneumothorax, in which conditions similar organisms, as in the sputum, can be demonstrated. As a rule such an exudate results from the direct extension, with rupture of a gangrenous cavity into the pleural cavity.

Bronchopneumonia, with no tendency to softening or gangrene, may occur in the previously uninvolved portions of the same lung or in the opposite lung.

A striking complication, peculiar to the fusospirochete pulmonary infection, is the development of a single or multiple metastatic putrid abscess in the cerebrum, apparently through the blood stream. Focal symptoms, motor and sensory, developing in the course of abscess in bronchiectasis would indicate such involvement. A terminal acute meningitis usually due to the streptococcus may also arise from extension to the meninges.

#### DIAGNOSIS

The diagnosis of fusospirochete infection depends on the proper examination of the sputum, together with clinical evidences of pulmonary involvement. The sputum should be collected over a period of twenty-four hours. The quantity is variable, but in instances where drainage into bronchi is open, as much as from 300 to 500 c c, or more, may be collected each day. When specimens are being obtained, the patient should be instructed to brush the teeth several times a day and frequently employ a mouth wash. If these precautions are taken, the anaerobes normally about the mouth will be reduced in number and will be less readily mistaken for the same organisms that may occur in the sputum. The odor is variable. At certain stages of abscess and bronchiectasis, the odor may be slight, at other times it becomes foul. In gangrene, it is always very putrid. When profuse in quantity the sputum forms three layers, an upper frothy and mucopurulent, middle transparent and viscid and lower gray or green. In all layers the same organisms can be demonstrated, although in the bottom they may be



more numerous Examination of a fresh specimen may reveal fatty acid crystals, tissue debris, pus, elastic tissue, and masses of bacteria To determine the type of bacteria, the sputum should be washed in several dishes of saline solution and smeared on the slide gently in order not to distort the spirochetes From 5 to 10 per cent carbolfuchsin for five minutes or the Fontana method for staining spirochetes may be employed Pleomorphic forms of fusiform bacilli, particularly the ordinary straight, curved and short comma types, together with spirochetes and streptococci are the most common combination of organisms observed (Fig 16) In several instances, fusiform bacilli with no or very few spirochetes were found In such, repeated examination may reveal spirochetes In this connection, it should be emphasized that the absence of spirochetes in the sputum does not eliminate the possibility of their presence in the lung In the discussion of the bacteriology, it was pointed out that there is often a definite distribution of these bacteria in the tissues with fusiform bacilli, cocci, few spirochetes in the pyogenic membrane, and spirochetes most numerous at the margin of abscess wall If the fusiform bacilli are numerous in the sputum one can reasonably presume that the symbiotic spirochetes are associated in the pulmonary lesion

Among the important symptoms the foul breath may be misleading A similar odor may be detected in diseased tonsils, carious teeth and gingivitis In these conditions, the same bacteria are generally the underlying cause In interpreting foul breath as a symptom of pulmonary involvement, the mouth as a source of odor should be eliminated Physical signs of pulmonary involvement are variable owing to the extent of the lesion and the frequency of involvement near the hilum Often the findings are few or indefinite, yet in the roentgen-ray film an abscess of considerable size may be clearly demonstrated Fluid in the pleural cavity may obscure the findings in the underlying lung

In differential diagnosis the pulmonary conditions due to other spirochetal infections should be considered Castellani<sup>10</sup> described the spirocheta bronchialis occurring in pulmonary hemoptysis chiefly in the tropics The expectoration is thin, odorless, watery and often a vivid pink color The spirochetes, according to Fantham,<sup>11</sup> differ from Vincent's types They are more actively motile, die more quickly, stain less readily, and produce coccoid bodies The Wassermann reaction is negative, blood count normal, and physical and roentgen-ray signs very scant<sup>12</sup> The condition responds well to sodium cacodylate and neo-arsphenamin and leads to rapid recovery Apparently in typical

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10 Castellani, A, and Chalmers, A J J Trop Med **22** 1882-1886, 1919

11 Fantham Ann Trop Med & Parasitol **9** 391-412, 1915

12 Violle, H Presse med **39** 359-361, 1918

acute cases, the pulmonary infection is due to the specific spirochetes of Castellani, but the more chronic types that have been described as due to the same spirochetes are erroneously reported, resembling more the fusospirochete type of pulmonary involvement that we have encountered. Confusion may arise if only spirochetes are sought for in the sputum, in our series we have never failed to find fusiform bacilli when spirochetes occurred.

Pulmonary syphilis has been reported in patients presenting solid shadows in the roentgen-ray film of the chest, a positive Wassermann and clearance under arsphenamin therapy. In an analysis of such reports, the clinical picture is frequently one of suppuration and gangrene. In our own experience, we have not observed solid lesions or gummas in the lung, even in individuals with positive evidence of syphilis in other viscera. In fusospirochete infection, the Wassermann is negative. In one instance, a positive Wassermann was obtained, but the syphilis in this patient was coincident. Furthermore, fusospirochete infection appears to respond readily to arsenic therapy. From our studies, we believe that the interpretation of pulmonary syphilis has been based on evidence that points to a lesion often due to fusospirochete infection.

Not all pulmonary conditions with foul sputum are due to the fusospirochetes. We have observed intensely foul expectoration in a patient with tuberculosis and secondary infection with *B. pyocyaneus*, another in which a small gram-negative anaerobic bacillus was obtained in cultures at necropsy. Foul smelling abscesses of the lung have been encountered from which colon bacilli were isolated in a patient with pelvic peritonitis. Such organisms causing foul lesions in the lung are exceptional, but should be considered where the fusospirochetes are not demonstrable.

In all patients with putrid expectoration, possible underlying predisposing lesions should be investigated. Tuberculosis, carcinoma, or foreign bodies may be overlooked if the sputum and foul expectoration alone are considered. Physical and roentgen-ray examination may reveal such associated pathologic changes. The error made is often the reverse, that is, to recognize the tuberculosis, or foreign body and to disregard the possible complication of abscess or gangrene which may be the more serious condition.

The course and duration of fusospirochete infection is extremely variable. The acute abscess may rupture in two or three weeks suddenly into the bronchus with profuse expectoration for a day, with rapid recovery. Some drain more slowly but disappear spontaneously in from two to four weeks. A considerable number become chronic with periods of improvement and recurrence of symptoms. Multiple abscess formations are less favorable and may rapidly terminate fatally or develop into

a chronic state Gangrene may be fatal within a period of from two to four weeks, or become a chronic condition lasting many months, with an unfavorable outcome

Bronchiectasis complicated by fusospirochete infection behaves irregularly In some, the putrid expectoration is constantly present, while in others it appears for a few weeks at intervals of months or years In the interval profuse odorless expectoration often persists, and in the sputum the anerobes can still be demonstrated In both bronchiectasis and chronic abscess formations, these organisms apparently persist as opportunists in the cavitations or tissues, and under certain conditions become pathogenic with the development of recurrences of symptoms of fever, foul expectoration and signs of consolidation

The prevention of pulmonary abscess and gangrene will depend to a considerable extent on the elimination of sources of infection It is, of course, impossible to remove completely the fusiform bacilli and spirochetes from the oral cavity, but much can be done to reduce the number of such organisms The teeth should be free of excessive tartar deposits Pus pockets, carious teeth, pyorrhea, in which conditions these bacteria occur in great abundance should be properly treated Tonsils in which masses of these organisms are prone to accumulate are best removed In some, expression can be employed Such procedures are especially indicated in the patient about to undergo anesthesia tonsillectomy, and in patients with chronic bronchitis, bronchiectasis or pulmonary tuberculosis

#### TREATMENT

Arsenic, particularly arsphenamin has been employed in fusospirochete infection of the mouth In stubborn cases of Vincent's angina, good results have been obtained Plaut<sup>13</sup> extended its use in stomatitis and in pulmonary gangrene Gerber<sup>14</sup> reported its use locally in Vincent's angina and gingivitis Peemoller<sup>15</sup> reported one case of fusospirochete pulmonary gangrene treated successfully with arsphenamin, and reviewed eight cases of gangrene treated similarly by Hirsch, Weiss and others

Our experience has shown favorable results with neo-arsphenamin in pulmonary abscess, from 0.3 to 0.9 gm was administered once a week It is, of course, recognized that abscesses frequently heal spontaneously when the drainage is good However, the improvement in several instances definitely followed the medication In Case 9 no treatment was given for five weeks The clinical and roentgen-ray findings

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13 Plaut, H C *Deutsch med Wchnschr* 3 117, 1914

14 Gerber *Deutsch med Wchnschr* 45 913, 1919

15 Peemoller, F *Deutsch med Wchnschr* 48 680 (May 26) 1922

indicated that the lesion had not improved but had even extended into the periphery. The introduction of neo-arsphenamin directly improved his condition, and in four weeks the fever disappeared and physical and roentgen-ray examinations demonstrated considerable resolution in the lesion. In Case 1 the patient was becoming progressively worse, although she was expectorating foul sputum (Fig 1). The temperature just before treatment was 103°. A single dose of neo-arsphenamin was followed by quick improvement, normal temperature three days later, less expectoration and complete clearance of the lesion occurred in three weeks (Fig 2). The more chronic types did not respond as readily, and some showed no definite change.

In bronchiectasis, the therapy can only influence the complicating infection by the anaerobes, and prevent possibly the formation of new cavitations. Distinct improvement with disappearance of foul smell of sputum, less fever and clearance of lesions was observed, but the cavities, of course, remained. No permanent results can be expected for this reason. Patients returning with recurrence of the symptoms require additional treatment.

In gangrene, we have not had the opportunity of treating early cases. In the far advanced stage the neo-arsphenamin apparently for a time caused diminished expectoration and some favorable changes in constitutional symptoms, but the toxemia ultimately overwhelmed the patient. It is evident that to obtain recovery in gangrene, the disease must be treated early. We are of opinion that a patient with pulmonary abscess and gangrene should have the benefit of arsenical treatment before more radical procedures such as pneumothorax and surgery are instituted. When surgery is necessary, arsphenamin should be combined in the treatment.

#### SUMMARY

1 Thirty-seven cases of pulmonary infection due to certain anaerobes, characterized by abscess formation and gangrene, are reported. The bacteriologic, pathologic, and clinical studies indicate a type of infection which may be classified as a distinct clinical entity. We refer to the process as a fusospirochete pneumonia, but pyogens, particularly streptococci, play an important contributory rôle.

2 The lesion is largely in the form of simple or multiple abscesses, gangrenous bronchopneumonia or a diffuse form of gangrene. The development of this type of infection depends to a great extent on predisposing factors such as general anesthesia, tonsillectomy, aspiration of foreign bodies, perforating lesions into the trachea and bronchi, infections, especially pneumonia, carcinoma, tuberculosis, and bronchiectasis and circulatory disturbances of various kinds. In a few the lesions develop without evident predisposing causes.

3 The clinical picture and course is variably influenced largely by the underlying contributory factors, resistance of the patient, and the extent of the lesion

4 Probably in all cases the sources of infection relate back to the teeth and tonsils where the fusiform bacilli and spirochetes and cocci are present in enormous numbers. The prevention of these pulmonary infections, therefore, lies in the proper hygiene of the mouth

5 Arsenic, particularly neo-arsphenamin, has a definitely therapeutic action on fusospirochete infection. Most favorable results are obtained in the early cases

# THE EFFECT OF IODIN IN EXOPHTHALMIC GOITER<sup>\*</sup>

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At a meeting of the Association of American Physicians in May, 1923, Plummer<sup>1</sup> reported on the use of iodine (compound solution of iodine) in the treatment of exophthalmic goiter. Iodine has been used in this disease by many in the past but has for the most part fallen into disrepute. Plummer, however, claimed striking benefit from its use. Following this suggestion we began shortly afterward the investigation which is reported in this paper. It is a continuation of the studies of various forms of therapy in exophthalmic goiter that have been made during the last ten years at the Massachusetts General Hospital.<sup>2</sup> Our results seem to be similar to those obtained in the Mayo Clinic, which have been recently published by Plummer and Boothby.<sup>3</sup>

The chief effect is what may be called the iodine remission. Trousseau,<sup>4</sup> in 1863, achieved this same result when he inadvertently gave a patient with exophthalmic goiter tincture of iodine in place of tincture of digitalis. He says "In the course of October, 1863, I was consulted by a young married lady, who habitually resides in Paris. She was suffering from subacute exophthalmic goiter. The bronchocele was of great size. When I examined her for the first time, although I had let her rest for a long while, and although I repeated the examination several times, and at sufficiently distant intervals, so as to make sure

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<sup>\*</sup> From the Thyroid Clinic of the Massachusetts General Hospital.

<sup>\*</sup> This article is No. 29 in a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses of this investigation have been defrayed, in part, by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.

1 Plummer, H S. Results of Administering Iodine to Patients Having Exophthalmic Goiter, *J A M A* **80** 1955 (June 30) 1923.

2 Means, J H, and Aub, J C. A Study of Exophthalmic Goiter from the Point of View of the Basal Metabolism, *J A M A* **69** 33 (July 7) 1917. Means, J H, and Holmes, G W. Further Observations on the Roentgen-Ray Treatment of Toxic Goiter, *Arch Int Med* **31** 303 (March) 1923. Richardson, E P. Relative Value of Surgery and Roentgen Ray in the Treatment of Hyperthyroidism, *J A M A* **80** 820-825 (March 24) 1923. Segall, N H, and Means, J H. The Immediate Effect of Subtotal Thyroidectomy in Toxic Goiter, *Arch Surg* **8** 176-187 (Jan) 1924.

3 Plummer, H S, and Boothby, W M. The Value of Iodine in Exophthalmic Goiter, *J Iowa M Soc* **14** 66 (Feb) 1924.

4 Trousseau. Clinical Lectures, Vol 1, p 587, Translation by P V Bazire, London, The New Sydenham Society, 1868.

that she was no longer under the influence of emotion, I still found her heart beat at the rate of 140 to 150 times in the minute. I recommended hydropathy and I wished to administer at the same time tincture of digitalis, but preoccupied with the idea that there would be some danger in giving iodine, I wrote iodine instead of digitalis, so that the patient took from 15 to 20 drops of tincture of iodine a day for a fortnight. When she then came back to me, her pulse was only 90. I found out my mistake, and I substituted tincture of digitalis for that of iodine, but, after another fortnight, the pulse had again gone up to 150, so that I at once returned to the iodine." This behavior of the pulse in exophthalmic goiter (and of the basal metabolic rate also, as we now know), has been frequently observed during the last year exactly under iodine as it was by Trousseau sixty years ago.

#### CASES STUDIED

Since May, 1923, forty-two cases of exophthalmic goiter have been treated with iodine, as compound solution of iodine, at the Massachusetts General Hospital. Of these, seventeen were outpatients, who reported frequently to the metabolism laboratory to be observed. The conditions under which they were followed were, of course, less uniform than those of the patients who were in the hospital. Of the latter, there were twenty-five. These patients were kept in bed continuously. Most of them were being prepared for operation. No patient of either group was considered to have adenomatous goiter with hyperthyroidism. Some did not have exophthalmos, but in these the symptoms were still thought to be due to what is termed "toxic hyperplasia," and this diagnosis was confirmed anatomically after operation.

#### ADMINISTRATION OF IODINE

Liquor Iodii Compositus, U. S. P., has a most objectionable taste, but all of the patients soon became accustomed to taking it by mouth. In no case was it necessary to give it per rectum as Plummer and Boothby have done in some emergencies. It was given after meals, well diluted with water. The mouth was rinsed at once after taking. The usual dose by mouth was 15 drops daily. Forty-five drops a day has been tried in two cases, but is apparently not much more effective than 15. The problem of the quantity of the dose in relation to various factors, such as the size of the gland, rate of metabolism, age of the patient, pathology of the goiter, duration of the disease, and the sympathomimetic symptoms, is yet to be solved. The parenteric routes of administration have not been studied. We gave one patient a solution<sup>5</sup> of iodine in mineral oil without potassium iodide and the result was

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<sup>5</sup> Devised by Dr. James L. Stoddard.

similar to those obtained with compound solution of iodin. The duration of medication has been from ten days to six months in individual cases.

### METHODS

The effects of treatment were followed by determinations of basal metabolic rate, pulse and weight. The Roth-Benedict apparatus was used. Precautions for preserving or producing basal metabolic conditions were taken.

### ANALYSIS OF DATA

An abrupt remission of the disease, evidenced by fall of metabolic and pulse rates, increase of weight, and diminution of symptoms was the immediate result of the administration of iodin in more than 80 per cent of our patients. This remission was most likely to occur in those patients who were resting in bed in the hospital without marked

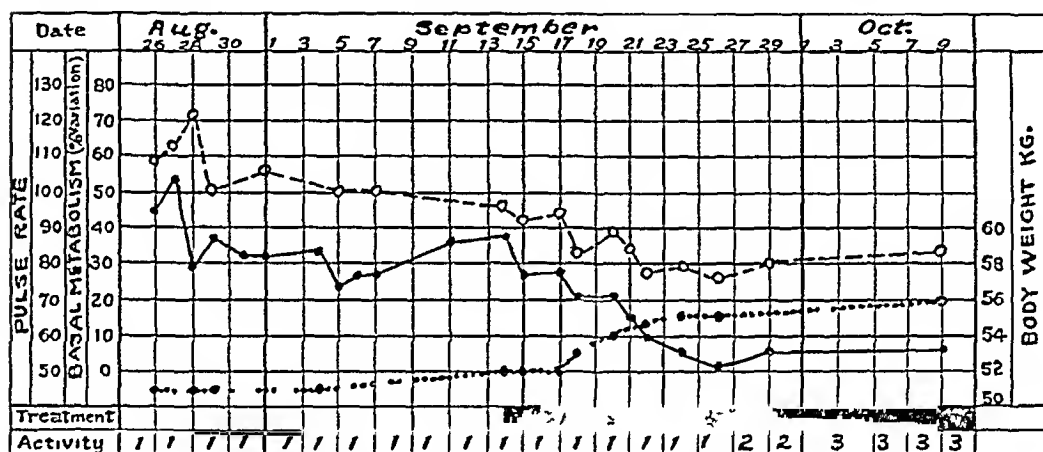


Chart 1—Typical iodin remission in exophthalmic goiter. Solid line is basal metabolic rate in percentage variation above normal which is 0. Dash line is pulse rate per minute. Dotted line is weight in kilograms shown at right. Activity 1 is complete rest in bed, 2 is partial rest, 3 is usual mode of life. From August 26 to September 14 no treatment but rest in bed was given. On September 14 compound solution of iodin, 15 minims daily, was begun and given thereafter daily, as indicated by the solid black in the treatment space.

physical or psychic complications. It did occur, however, in outpatients, but was then less rapid and less marked.

The findings in a patient who had a typical abrupt remission are shown in Chart 1. The history is as follows:

### REPORT OF CASE

M. M., a woman, aged 23, first noted fatigue, nervousness, palpitation, dyspnea, diarrhea, and tremor in September, 1922. The goiter was perceptible in the following Spring. She entered the Massachusetts General Hospital in August, 1923, with exophthalmos, lagging lid, a diffuse symmetrical goiter which had a thrill and bruit, a moist skin, tremor and tachycardia, and a basal metabolic rate of plus 45 per cent, pulse rate of 110 per minute, and weight



51.5 kg The patient remained at complete rest in bed in the hospital for one month After three days the basal metabolic rate was plus 38 per cent Two weeks later, without any medication, the rate was again plus 38 per cent, pulse rate 95, weight 52 kg This period of two weeks forms an excellent control period Fifteen minims of compound solution of iodin was now given by mouth daily No other change in treatment was made During the next twelve days the basal metabolic rate rapidly decreased until it reached plus 1 per cent, the pulse rate became 78 per minute and the weight increased to 55 kg The patient appeared much quieter with less exophthalmos and tremor She said she felt well

Remissions of this character were frequently as rapid and as extensive as those which follow subtotal thyroidectomy Chart 2 shows the daily basal metabolic rate curves of eight patients There is a control period of five days The points at which daily iodin administration

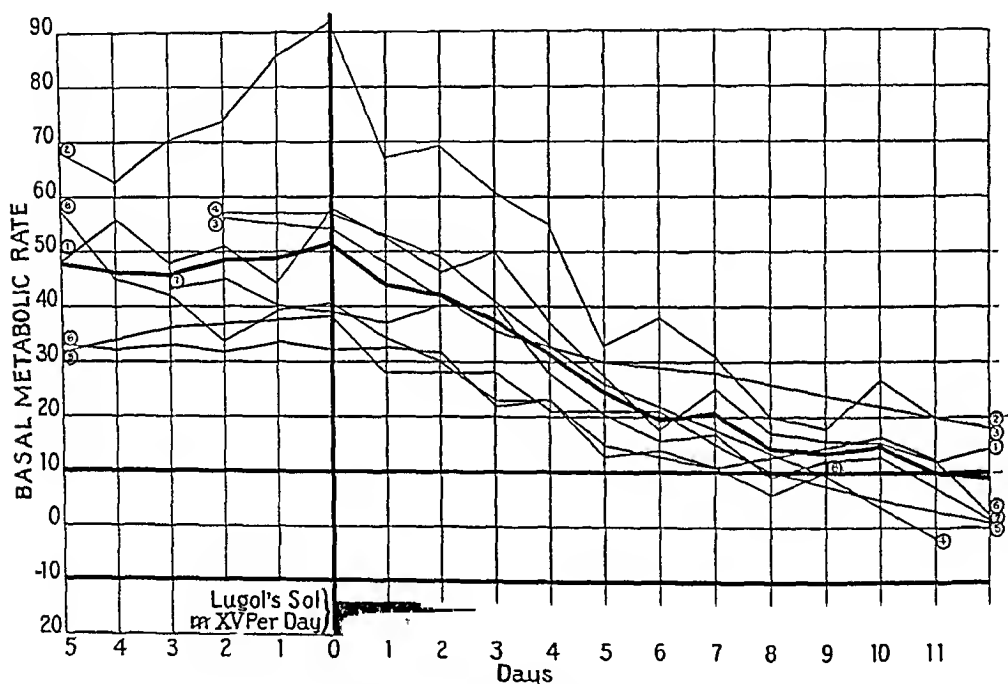


Chart 2—Curves of basal metabolism of eight patients with exophthalmic goiter given iodine daily, beginning with zero line Average curve, solid black double width

was started are plotted on the zero line The basal metabolic rates in all these cases decreased rapidly during the next ten days The line representing the average of this group is double width On the day of beginning iodine treatment it is at a level of plus 51 per cent On the tenth day afterward it is at plus 14 per cent This gives an average rate of detoxication of about 3.7 points daily This is nearly the same rate of detoxication that Segall and Means<sup>2</sup> found after subtotal thyroidectomy By daily metabolic rate measurements of patients before and after operation, they determined accurately that the rate of detoxication is about 3.7 points a day The average curve of their group of

eleven is at plus 45 per cent the morning before operation. During the next ten days after a postoperative peak, it falls rapidly to plus 8 per cent. It is a most important theoretical and practical fact that compound solution of iodine will have in many cases of exophthalmic

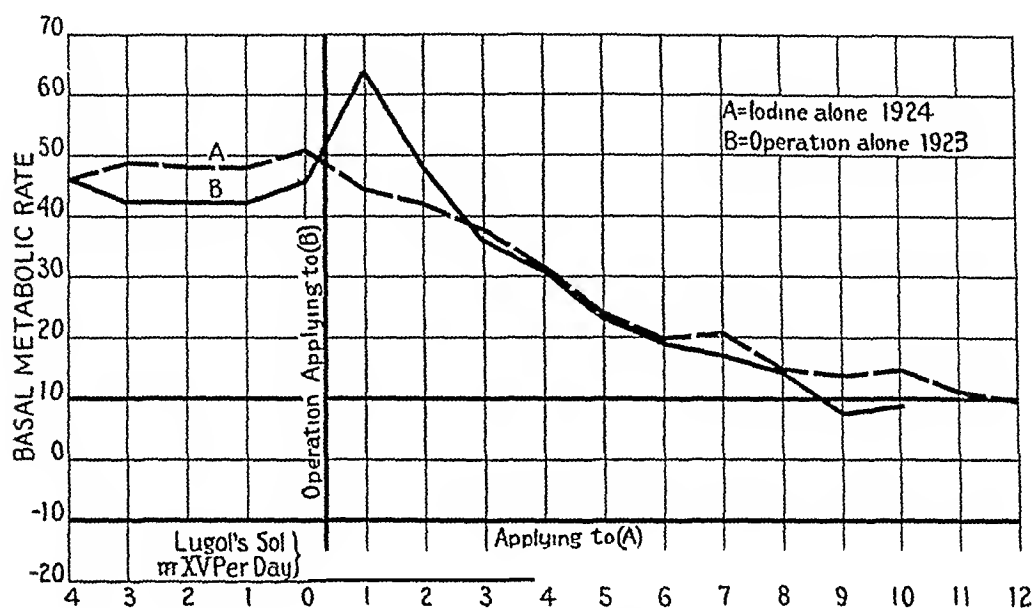


Chart 3—The average curve obtained by Segall and Means showing effect of subtotal thyroidectomy is a continuous line, the average curve showing the effect of iodine alone (Chart 2) is an interrupted line. Note the absence of the postoperative peak in the latter curve, but that otherwise the curves are nearly superimposed.

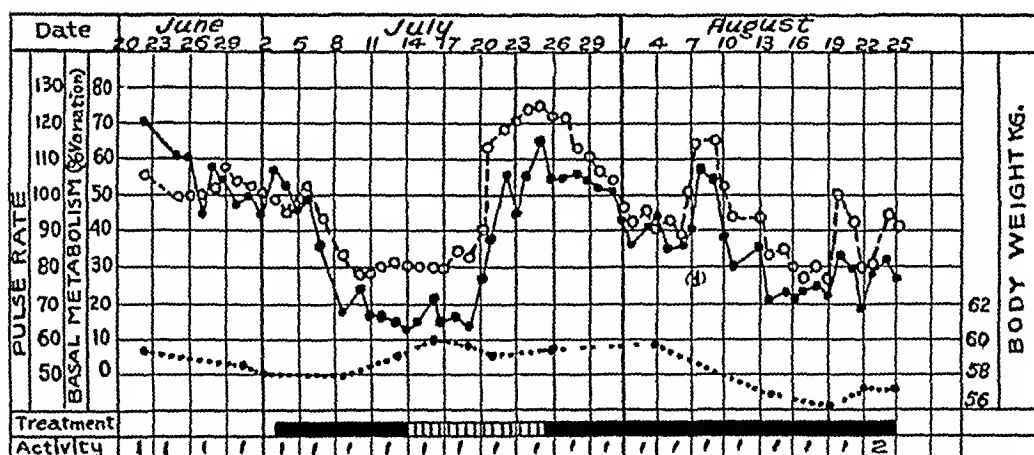


Chart 4—Repeated iodine remission. Solid line, metabolism. Dash line, pulse. Dotted line, weight. Treatment was rest until solid black band, indicating compound solution of iodine, 15 minims per day. Placebo indicated by cross bars, from July 14 to 25, during which time there was abrupt recurrence. Iodine restarted. (1) indicates hemithyroidectomy. Activity 1 is rest in bed.

goiter (48 per cent of our series) the same immediate effect on metabolic rate as removing five-sixths of the gland. The average curves of the effects of iodine and of operation are charted together (Chart 3) to emphasize their similarity.

The demonstration of iodin as the causal agent of this remission, we think, is completed by the fact that substitution of a placebo during the remission is followed by abrupt recurrence, and in addition, that if iodin is again started a second remission is produced. We have observed this in four cases, two of which are illustrated in Charts 4 and 5

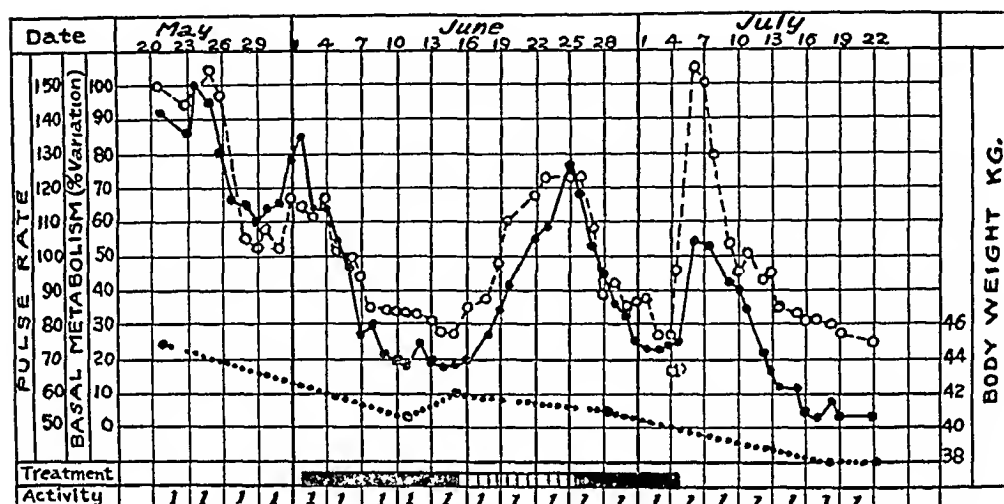


Chart 5—Repeated iodine remission. Black band in treatment is iodine, cross bars, placebo. (1) is subtotal thyroidectomy

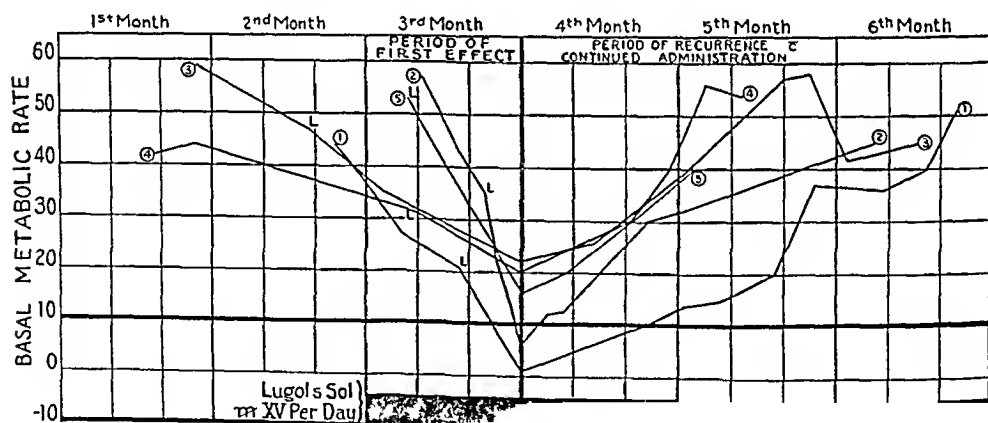


Chart 6—Remission and recurrence under iodine. Five metabolism curves remission shown by fall of metabolic rate to the central ordinate. Compound solution of iodine started in the individual cases at L. Recurrence shown by rise of the metabolism curves during succeeding three months

That such a remission is not maintained by continued administration of iodine when the patient returns to daily life is shown in the continuation of the history of M. M., described in the foregoing

One week after reaching a normal level of basal metabolism the patient returned to her studies as a senior in college. A month after this, although taking iodine every day, the basal metabolic rate was plus 13 per cent, pulse 95, weight 56 kg. Toward the end of the second month the basal metabolic rate

was plus 30 per cent, pulse 100, weight 56 kg. Toward the end of the third month, the basal metabolic rate was plus 52 per cent, pulse 117, weight 56 kg.

A similar prolonged recurrence was observed in four other patients also taking 15 minims of compound solution of iodin daily for from two to four months. Chart 6 shows the curves of these five patients. The lowest points, indicating the initial effect of iodin, are synchronized. The subsequent recurrence with continued iodin administration is well

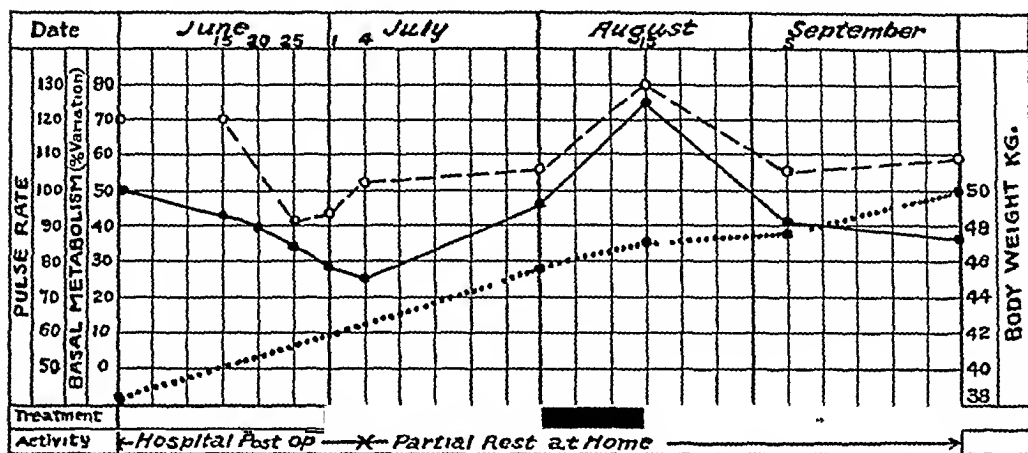


Chart 7—Post-iodin reaction. Metabolic rate, solid line, pulse rate, dash line, weight, dotted line. Iodin indicated by solid band in treatment space is compound solution of iron, 15 minims per day, given from June 29 to August 1, omitted from August 1 to 15, restarted on August 15.

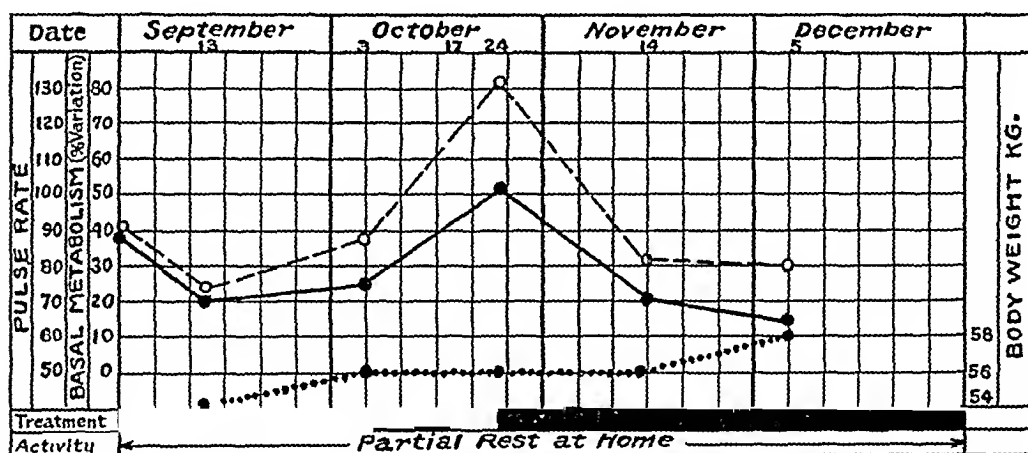


Chart 8—Post-iodin reaction. Iodin omitted by patient from October 17 to 24.

shown. They reach their original levels in from one to two months. None of these patients were resting in bed. The dosage throughout was unchanged. It is to be noted that there is no period of uniform level of metabolism during this remission. The recurrence begins at once, its rapidity is variable, and the period within normal limits may be very brief, amounting to only a few days, so that if operation is contemplated action must be taken at once while the primary effect of

iodin is predominant Because of this recurrence under iodin, we believe that as now used iodin is not a cure for exophthalmic goiter, and that it should not be used with this expectation

The way in which iodin produces this remission in exophthalmic goiter is far from clear Plummer's<sup>1</sup> theory, that it lies in the iodizing of abnormal thyroxin, is not entirely convincing For one thing it should be noticed that the dose of iodin given is relatively very great,

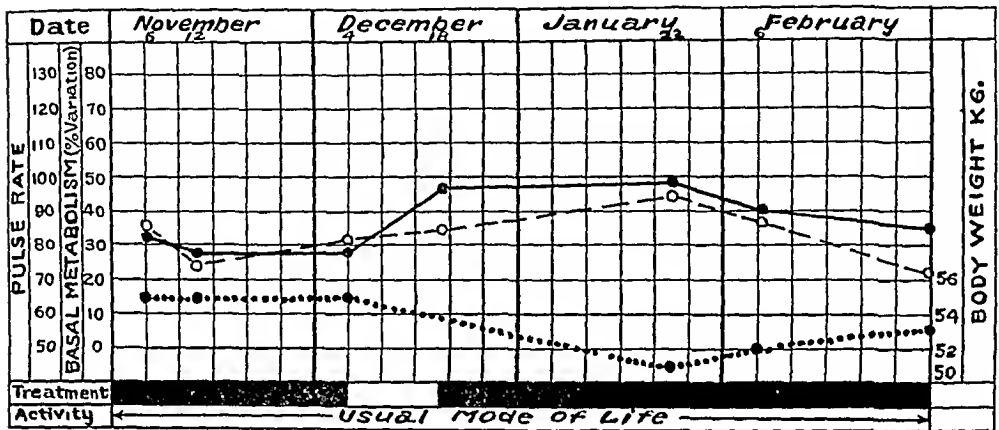


Chart 9—Post-iodin reaction Iodin ineffective during November, omitted December 4, restarted December 18

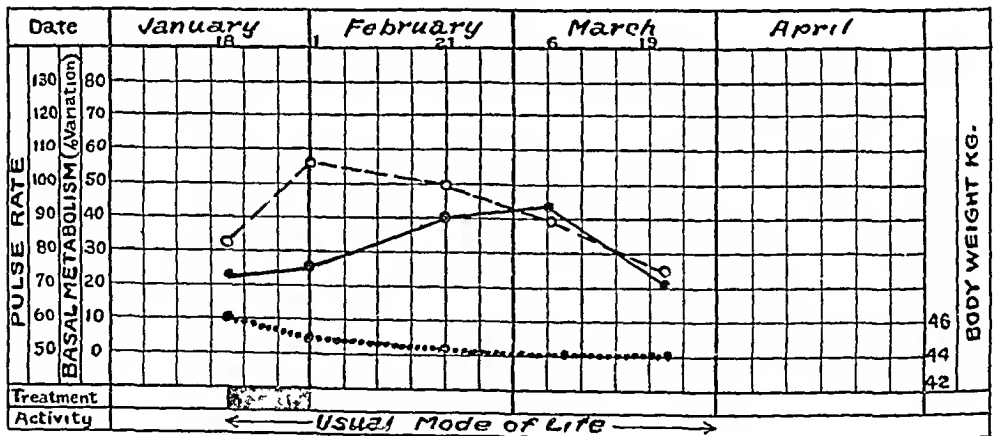


Chart 10—Post-iodin reaction Iodin given January 18 to February 1, followed by rise of metabolic rate to plus forty with subsequent return in March to its previous level about plus twenty

fifteen minims of compound solution of iodin is equivalent to 125 mg of iodin The amount of thyroxin iodin necessary to keep the body at a basal metabolic rate of plus 50 is only 2 mg daily,<sup>6</sup> yet doses smaller than 15 minims a day of compound solution of iodin are not as effective In addition, we have observed (Chart 6) recurrence of the

<sup>6</sup> Plummer, H S Interrelationship of Function of the Thyroid Gland, J A M A 77 243 (July 23) 1921

original disease while the patient was taking this dose, which is enormous when compared with the amount of iodine needed for thyroxine

After a patient with exophthalmic goiter has been taking iodine, we have found that a rapid rise of metabolic rate and increase of toxic symptoms occur if the iodine is omitted. And this happens whether or not this omission takes place while the iodine is producing its first effect or during the secondary recurrence with continued administration. Illustrations of the former have been shown in Charts 4 and 5. Illustrations of the latter are given in Charts 7, 8, 9 and 10. In Chart 7 it will be noted that the metabolic rate is apparently increasing in spite of the iodine, yet when it is discontinued a still more rapid rate soon is found, but when the iodine is again given, a rate at the former level is subsequently reached. This brings out the very important practical

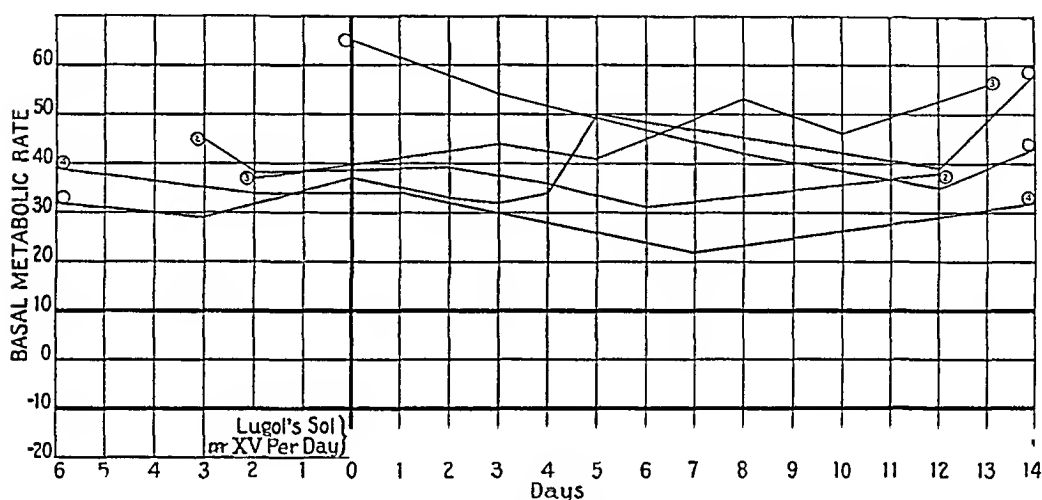


Chart 11—Metabolism curves of five patients with exophthalmic goiter, in which iodine was without observable effect. All patients resting in bed. Compare with Chart 2.

point if iodine is used as preoperative preparation, whether it is successful or not, no gap between medication and operation should be allowed to occur. We have observed this further sudden increase on discontinuance of the iodine in many instances.

In this connection it is of interest that previous iodization in no way prevents the toxic effect of thyroxine. This has been shown in rabbits by Sturgis.<sup>7</sup> In human beings it has been found by one of us (HLS) that the taking of iodine in no way reduces the thyrotoxicosis induced by thyroid ingestion, nor accelerates the rate of recovery therefrom.

Some of our patients showing exophthalmos, and in which a hyperplastic thyroid was later found at operation, did not show the iodine remission. A chart (Chart 11) of the metabolism curves of five such

<sup>7</sup> Dr. C. C. Sturgis, Boston. Personal communication.

patients is shown. They were all in the hospital under identically the same conditions as those illustrated in Charts 1, 2, 4 and 5, and were given the same dosage of iodine for a period which in the others produced marked effects. It is to be noted that these curves remain practically horizontal and form a control group as to the rest factor, which might have accounted for some of the drop in the first cases cited. The pathologic reports of the cases of this unsuccessful group all show follicular hyperplasia without adenomas. No criterion for accurately differentiating this unsuccessful group from the successful has been found.

As to the probability with which a successful result with iodine is to be expected, it is of course impossible to make anything but a rough approximation from such a small number of cases. The number which we have studied which were treated identically is twenty-five. Of these we have pathologic reports on the thyroid gland in all but two cases. The reports indicate the absence of adenoma and the presence of generalized follicular hyperplasia. Of these twenty-five cases, twenty (80 per cent) responded to iodine by a more or less extensive remission of the disease. Of these twenty, twelve (48 per cent) responded with the acute iodine remission resembling the effect produced by subtotal thyroidectomy. In the remaining eight (32 per cent) the remission occurred, but was less extensive. In five unsuccessful cases (20 per cent) two of the patients were pregnant and one had cardiac decompensation. If these are omitted from the calculation, iodine administration was successful in twenty of twenty-three, or 92 per cent of our hospital cases.

#### CONCLUSIONS

- 1 Iodine by mouth will produce abrupt remission in most cases of exophthalmic goiter.

- 2 The remission is often as rapid and as extensive as that following subtotal thyroidectomy.

- 3 It is believed that iodine is the causal agent of this remission.

- 4 Iodine alone as now used has not been shown to be sufficient to suppress the disease permanently.

- 5 After a patient with exophthalmic goiter has been taking iodine, a rapid rise of metabolic rate and increase of toxic symptoms will occur within one or two weeks if the iodine is stopped.

- 6 In some cases of exophthalmic goiter, iodine has no observable effect.

# A QUANTITATIVE INDEX OF KIDNEY FUNCTION

## THERMODYNAMIC CONSIDERATIONS IN THE ESTIMATION OF RENAL EFFICIENCY <sup>1</sup>

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MONTREAL

From the numerous data available, the deduction is that the chief function of the kidneys is to keep the composition of the blood constant. The kidneys must react to the various deviations from the normal composition of the blood by excreting water or substances dissolved in it. During the process of excretion work is done. All tests for renal efficiency are based on the ability of the kidneys to do their work. It is generally recognized that, since the complete mechanism of the secretion of urine is imperfectly understood, the total work done by the kidneys during this process cannot be accurately determined. Attempts have been made to estimate this work according to known physical principles. Of special note are the procedures of Dresser, Galeotti and Hill. The data thus obtained and some of the renal function tests now in use have been reviewed <sup>1</sup>

In a recent communication <sup>2</sup> a study was made of the value of the "urea concentration factor" in the estimation of renal efficiency. It was demonstrated that, at least so far as lesions associated with defective excretion of urea are concerned, the urea concentration factor, if determined under a uniform set of conditions described, is a more sensitive test for the detection of impairment in function than the other methods in common use. Further clinical experience with this test, employed routinely in practically all patients having an albuminuria admitted to the Montreal General Hospital has strengthened this view. So far, 610 observations have been made on 284 patients. The results are briefly recorded in Table 1. The blood urea was the least sensitive in the detection of early renal inefficiency, having been found increased in 341 or only 56 per cent of the total number of observations. The urine urea concentration test <sup>3</sup> was a better index than the blood urea. The "urea concentration factor" was the most sensitive, showing impair-

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\* From the Department of Metabolism of the Montreal General Hospital. This work was done with the aid of a grant from the Cooper Memorial Fund.

1 Cushny, A. R. The Secretion of Urine. Monographs on Physiology, New York, Longmans, Green & Company, 1917.

2 Rabinowitch, I. M. The Urea Concentration Factor in the Estimation of Renal Efficiency, Arch Int Med **32** 927 (Dec 1923).

3 MacLean, H., and de Wesselow, O. L. V. On the Testing of Renal Efficiency with Observations on the Urea Coefficient, Brit J Exper Pathol **1** 53 (Feb) 1920.



ment in 573 or 94 per cent of all the observations. The reason for this appears obvious. The earliest evidence of impaired function may be a diminution in the ability of the kidneys to concentrate. But during a day, by constant effort, the total end products of protein metabolism may be eliminated. Under these conditions the concentration of urea in the blood, the following morning in the post absorptive state, may be normal. The urine urea concentration test would thus be more sensitive than the blood urea. The reasons for the "urea concentration factor" being the most sensitive have been discussed in the previous paper.<sup>2</sup>

TABLE 1—Results of 610 Observations on 284 Patients

Test	No of Cases	Per Cent
Blood urea nitrogen increased	341	56
Urine urea concentration diminished	453	76
Urea concentration factor lowered	573	94

Briefly, the urea concentration factor is obtained as follows. No food nor fluids are allowed after six o'clock the evening before the test. At six o'clock the morning of the test the patient voids. This specimen is discarded. Fifteen grams of urea, dissolved in 150 c c water, are then given orally. No food nor fluids are allowed during the test. Blood is collected for analysis before and two hours after, and the urine one and two hours after the administration of the urea. Urea determinations were made on the blood and urine by the Van Slyke (urease) method. All determinations were made in duplicate. The urea concentration factor is represented by the formula

$$U C F = \frac{\text{Milligrams urea per 100 c c urine}}{\text{Milligrams urea per 100 c c blood}}$$

The choice of the blood and urine at the stated periods was, as noted by the author of the test,<sup>4</sup> purely arbitrary. The value of urea studies in the estimation of renal efficiency was pointed out in the discussion of the physiologic aspects of urea.<sup>2</sup>

However, as with the other tests in use, the urea concentration factor appeared to yield results of a qualitative nature only. Judging from the clinical picture, since the normal value for the factor was found to be approximately 40, because a factor of 20 was found, it did not appear that the efficiency of the kidneys could be regarded as being only 50 per cent of the normal.

The object of this communication is to present what appears to be a still more exact method of studying renal function, in that, at least so far as the excretion of one substance is concerned, namely urea, an attempt is made to express the results in quantitative terms. The "urea

<sup>4</sup> Harrison, G. A. On Urea Tests of Renal Function, Brit J Exper Path 3: 28 (Feb) 1922.

concentration factor" forms an essential part of the necessary data. It can be shown, mathematically, that considered from another point of view, the factor is, indirectly, a quantitative index, and also what appeared to be a purely arbitrary choice, that is, the periodic collection of the blood and urine, has a real basis. Because of the quantitative nature of the results the clinical value of this test is greatly enhanced. In the evaluation of any laboratory test for clinical use, clinical experience must be the final source of judgment. As in the physical sciences, if experience does not correspond to the deductions of a mathematical expression, either the reasoning is wrong or certain variables enter into the problem not recognized and therefore have been neglected. Experience so far with this test shows that the results obtained parallel more closely the clinical progress of the patient than the other tests in use. The basis of the test is the estimation of the work done by the kidneys, in the excretion of a definite amount of urea, by the application of certain elementary laws of thermodynamics. These will now be briefly considered.

#### BASIS OF THE TEST

The work done by a gas in expanding isothermally (that is, expansion at constant temperature) by a definite amount from a volume  $V_1$  to  $V_2$  is expressed by the equation  $W = R T \text{Loge} \frac{V_2}{V_1}$  or  $W = 2.3 R T \text{Log}_{10} \frac{V_2}{V_1}$  where  $W$  is the work done,  $R$  is the universal gas constant, and  $T$  is the absolute temperature. The numerical value for  $R$  is found from the general gas equation  $PV = RT$ . That is,  $R = \frac{PV}{T}$ , and depends on the units in terms of which  $P$  and  $V$  are expressed. For our present consideration  $P$  is expressed in terms of dynes per square centimeter and  $V$  in terms of cubic centimeters,  $R$  has therefore a value of 0.85 and  $W$  is thus expressed in terms of kilogram-meters. The fundamental importance of this equation is generally recognized in biologic studies, since it may be applied to solutions as well as gases.

We are now concerned with the work done by the kidneys in the excretion of a definite amount of urea, and changing the concentration of urea from that in which it exists in the blood to that in which it exists in the urine. By applying the foregoing formula, the work done by the kidneys is calculated as follows:

$$W = 2.3 R T \left[ \text{Log}_{10} \frac{C_1}{C_3} + \text{Log}_{10} \frac{C_2}{C_1} \right] \frac{m}{M}$$

Where  $W$  = kilogram meters work

$R = 0.85$

$T = 310 (273 + 37)$

$C_1$  = concentration of urea in the urine before giving the urea

$C_2$  = concentration of urea in the urine after giving the urea

$C_3$  = arithmetical mean of blood urea concentration before and after giving urea

$m$  = grams urea excreted during period of observation

$M$  = weight of one gram molecule of urea (60)

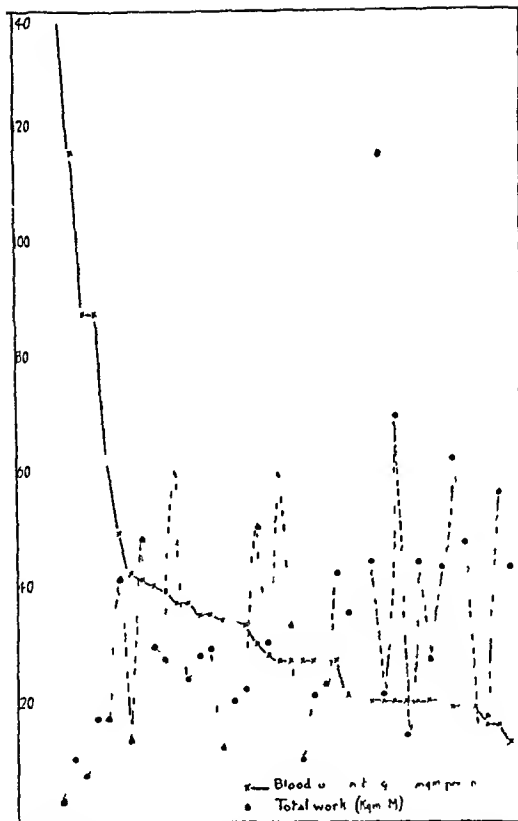


Chart 1—The relation between the blood urea nitrogen and total work done in two hours

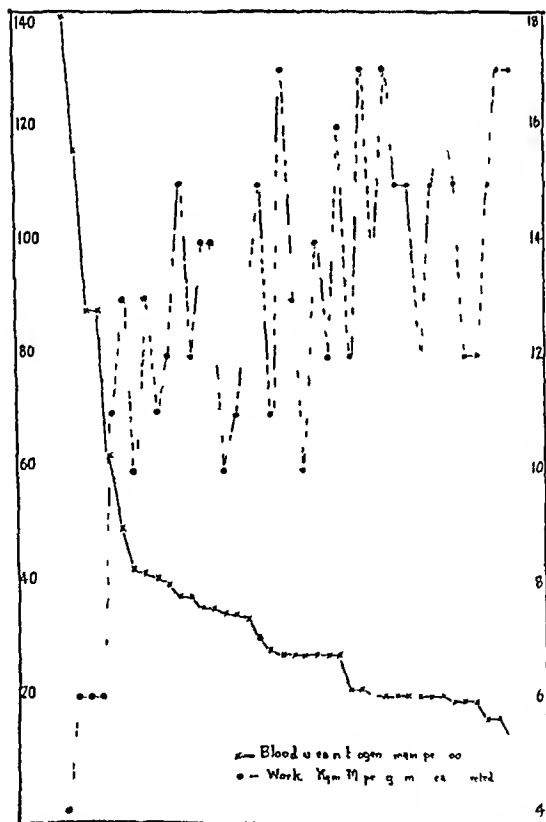


Chart 2—The relation between the blood urea nitrogen and the work done per gram of urea excreted

By reducing the formula to simpler terms, not only the application of the factor becomes apparent, but also the idea that the choice of the periodic collection of the blood and urine specimen is arbitrary is dispelled. Thus

$$W = 2.3 R T \log_{10} \left\{ \frac{C_1}{C_3} - \frac{C_2}{C_1} \right\} \frac{m}{M}$$

$$= 2.3 R T \log_{10} \left\{ \frac{C_2}{C_3} \right\} \frac{m}{M}$$

It will be noted that  $\left\{ \frac{C_2}{C_3} \right\}$  is the urea concentration factor

An example of the complete data involved in such a calculation is given in Table 2. These data were obtained from a normal person. It will be noted that the urea concentration factor is obtained in a slightly different manner from that previously described. The value of the arithmetical mean of the concentration of urea of both blood specimens is employed, instead of the one blood only. This procedure increases the value of the factor for normal persons from that of 40, previously recorded, to 50.

TABLE 2—*Calculation of Work Done in the Excretion of Urea in a Normal Subject*

Hour	Urine			Blood Urea Nitrogen, Mg per 100 C c	Factor	Work	
	C c	Urea, per Cent	Urea, Gm			Total Kilogram-meter	Kilogram meter per Gm Urea
1	75	3.08	2.31	21	49.7	70.4	17.1
2	60	2.98	1.80	35			
Total			4.11	Aver 28			

Under the uniform set of conditions described, a normal person excretes approximately from 3 to 5 gm of urea in two hours and the kidneys perform in this process from 50 to 85 kilogram-meters work, depending on the amount of urea excreted. But the work done per gram of urea excreted is remarkably constant, approximately 17 kilogram-meters. The importance of recognizing the variations due to the rate of absorption of the urea from the alimentary tract will be shown in the comment of the results.

Observations were made on patients showing an albuminuria. No selection of the cases was made clinically. The subjects included mild and advanced cardiac, renal, cardiorenal, surgical and urologic patients. These are shown in Table 3, which contains the data of the first 40 observations. Further tabulation seemed unnecessary. Chart 1 represents, graphically, the relation between the blood urea nitrogen and total work done in two hours. Chart 2 represents, graphically, the relation between the blood urea nitrogen and the work done per gram

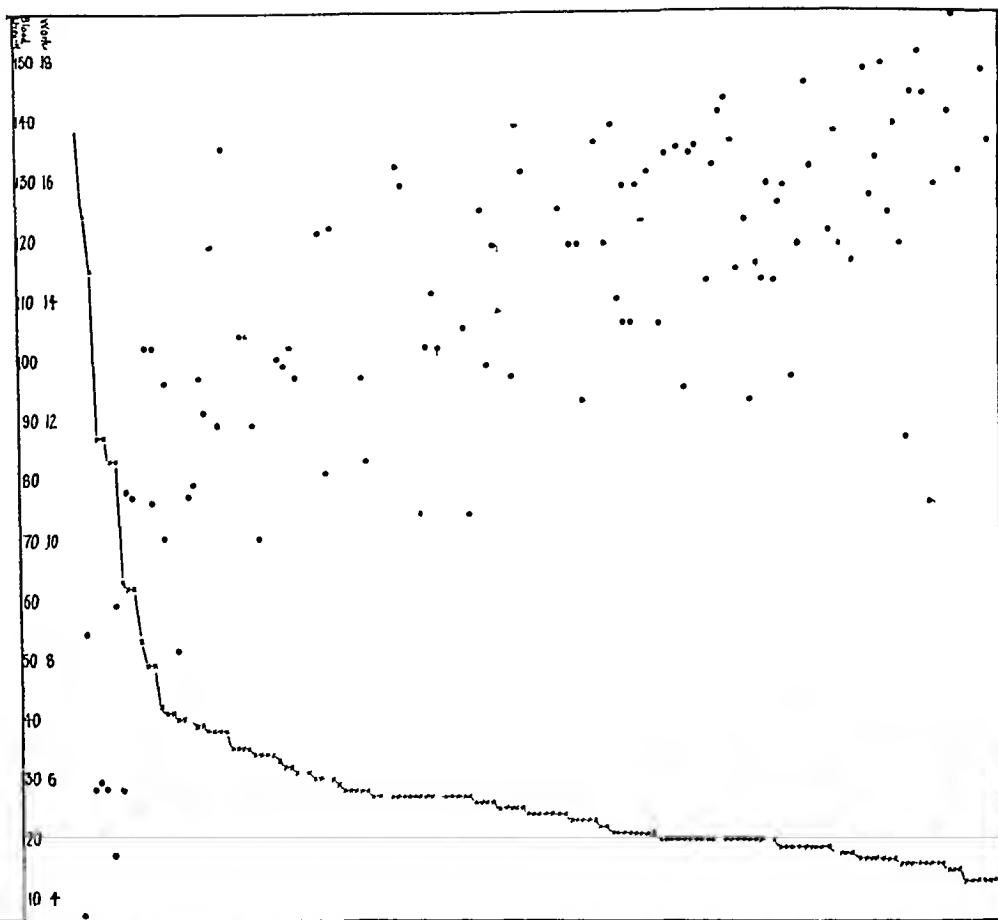


Chart 3—The relation between the blood urea nitrogen and work done per gram of urea excreted of all observations made

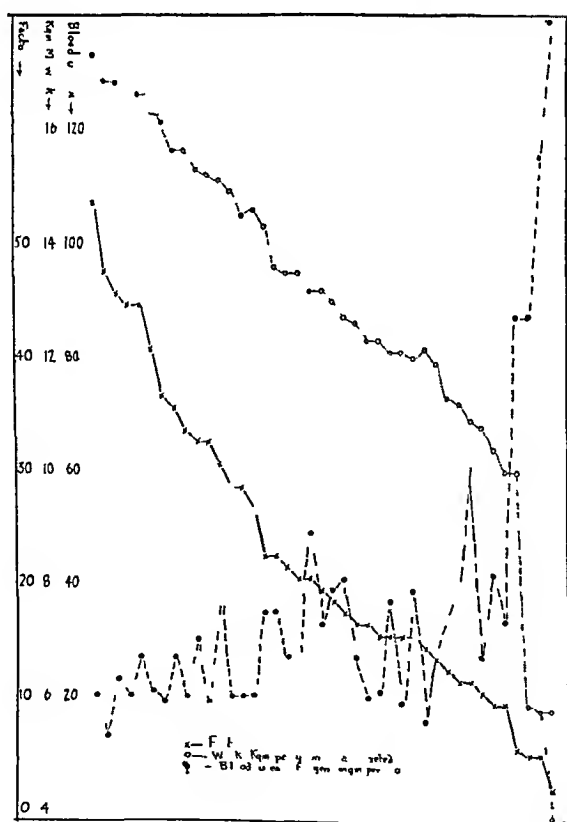


Chart 4—The relation between the urea concentration factor and the work done per gram of urea excreted

of urea excreted by the same subjects as shown in Chart 1 Chart 3 shows the relation between the blood urea nitrogen and work done per gram of urea excreted of all observations made Chart 4 shows the relation between the urea concentration factor and the work done per gram of urea excreted

TABLE 3—*Observations Made on Twenty-Nine Patients Showing Albuminuria*

Case	Hours	Grams Urea, in 2	First Blood Urea-Nitro gen	Aver age Blood Urea-Nitro gen	Per Cent Concen- tration Urea, Second Urine	Factor	Total Work, Kilo gram-meter	Work, Kilo gram meter per Gm	Clinical
1	1 31	35	49	1 08	10 2	13 2	10 0	Chronic nephritis	
2	3 02	88	93	0 80	4 0	18 1	6 0	Chronic preuremia	
	1 90	116	123	1 04	3 9	11 2	5 9		
	1 42	88	96	0 79	3 8	8 3	5 9		
3	2 57	21	25 5	2 94	53 9	44 7	17 4	Orthostatic albuminuria	
4	1 85	35	41	1 16	13 2	20 9	11 3	Pyelonephritis	
	2 24	21	25	0 92	17 1	27 7	12 4		
	2 53	28	32	1 44	21 0	33 6	13 3		
	4 20	21	24 5	2 38	45 4	70 1	16 7		
5	1 08	28	30	0 72	11 2	11 3	10 5	Vesical calculus	
6	2 24	22	27 5	2 42	41 1	36 2	16 2	Chronic nephritis	
7	2 12	36	40	1 99	23 2	29 0	13 7	Prostatic enlargement	
8	2 78	41	48 5	1 28	12 3	30 5	11 0	Pyelonephritis	
9	1 68	63	73 5	1 92	12 2	18 3	10 9	Prostatic pyelonephritis	
	2 23	36	46 5	2 25	22 6	30 3	13 6		
	1 79	34	38	1 62	19 9	23 4	13 1		
10	2 73	29	39	1 14	13 6	31 1	11 4	Prostatic enlargement	
	2 05	38	45	1 58	16 4	25 0	12 2		
11	1 66	28	35	1 68	22 4	22 5	13 6	Nephroptosis	
	2 60	14	17 5	1 80	48 1	43 9	16 9		
12	1 93	28	31 5	1 17	17 3	23 9	12 4	Cystitis	
13	1 40	20	24 5	0 85	16 2	16 9	12 1	Tuberculous kidney	
	2 30	40	43	1 53	18 6	28 2	12 8		
	3 18	20	28	1 94	32 6	48 3	15 2		
14	3 15	50	53	2 40	21 1	41 8	13 3	Gonorrhea	
15	1 01	21	25	1 53	28 6	14 7	14 6	Nephrolithiasis	
16	1 57	17	18 5	0 60	15 1	18 5	11 8	Chronic nephritis	
17	2 74	28	34	2 64	36 3	43 0	15 7	Chronic myocarditis	
18	2 93	21	24 5	1 80	34 3	45 1	15 4	Pyelonephritis	
19	0 93	140	144	0 81	2 5	3 6	3 9	Arteriosclerosis	
20	3 31	20	28	1 94	32 6	48 3	15 2	Ureteral stone	
21	3 77	28	31	3 02	45 5	62 9	16 7	Chronic nephritis	
22	4 15	38	36	2 40	31 1	62 2	15 0	Hematuria, tumor ?	
23	3 96	20	24 5	1 97	37 5	62 5	15 8		
24	3 80	17	27 5	1 80	30 6	57 0	15 0	Tuberculous epididymo orchitis	
25	1 65	24	28	2 76	46 0	27 5	16 7	Cardiorenal	
26	3 01	22	31	1 10	16 5	36 7	12 2	Chronic nephritis	
27	3 00	21	28	1 74	29 0	44 1	14 7	Myxedema	
28	3 85	42	49 5	1 94	18 3	48 8	12 7	Chronic nephritis	
29	1 38	43	50	1 08	10 0	13 9	10 1	Chronic nephritis	

## COMMENT

Charts 1 and 2 demonstrate that the total work done during a known period cannot be taken as an index of renal efficiency This is influenced by the rate of absorption of the urea from the alimentary tract The work done per gram of urea excreted does, however, indicate efficiency and varies, roughly, inversely as the concentration of urea in the blood From the previous considerations of the factors governing the retention of urea in the blood no strict relation is expected The factor of absorption of urea is demonstrated by the data in Table 4 The data were obtained from a normal individual, a laboratory worker, by giving him each morning on successive days 15 gm of urea The

total grams of urea excreted in two hours and the concentration of urea in the blood at the end of this period were noted. For these calculations it is assumed that urea is evenly distributed throughout the body fluids and that 1 kg of body substance contains approximately 700 c c of water. In this subject, therefore, each gram of urea absorbed from the alimentary tract should, if not excreted, increase the concentration of the blood urea nitrogen by 1.5 mg per hundred cubic centimeters. It will be noted that according to the above assumptions as much as 5 gm failed to be absorbed during one period.

TABLE 4—*Rate of Absorption of Urea*

Normal Subject		Weight of Body Fluids, 65 Kg			
Day	Urea Ingested, Gm	Urea Excreted, in 2 Hours	Blood Urea Nitrogen		Urea Not Absorbed, Gm
			Calculated	Actual	
1	15	5.12	15.0	14	0.65
2	15	4.11	16.7	14	1.70
3	15	4.77	15.7	7	5.60
4	15	4.71	15.8	8	5.00
5	15	5.16	15.1	11	2.60
6	15	4.67	15.8	10	3.70

When performed under the uniform set of conditions (post absorptive state, limited water intake, etc.) the normal amount of work done is regarded as 17 kilogram-meters per gram of urea excreted. That this value may be made to vary when the test is not performed under the conditions described is quite obvious. The data in Table 5 show the

TABLE 5—*Effect of Water Intake on Work Done (Normal Subject)*

Day	Water Intake, C c	Urine Urea Excreted in 2 Hours	Blood Urea Nitrogen, Average	Urine Urea Concentration Second Hour	Factor	Work, Kilogram meter per Gm Urea Excreted
1	150	5.12	28.0	3.12	52.0	17.3
2	250	4.11	28.0	2.98	49.7	17.1
3	500	4.77	24.5	2.16	41.1	16.2
4	1,000	4.71	25.0	0.78	14.5	11.7
5	1,500	5.16	26.5	0.49	8.6	9.4
6	2,000	4.67	26.0	0.42	7.5	8.8

effects of varying the amount of water intake. The test was performed under the standard conditions described except that each day the quantity of water taken was varied. On successive days the subject, a normal person, was given 15 gm of urea dissolved in 150, 250, 500, 1,000, 1,500 and 2,000 c c of water, respectively. It will be noted that varying the quantity of water did not effect the rate of urea excretion. This has previously been demonstrated.<sup>5</sup> The effect was to lower the value of the urea concentration factor, and thus lower the amount of work done. It appears that this observation may have some therapeutic

<sup>5</sup> Addis, T., and Drury, D. R. The Rate of Urea Excretion, J Biol Chem 55: 639 (April) 1923.

significance By increasing the water intake and making the kidneys excrete a less concentrated urine the same amount of urea was excreted with less work It is here assumed that the excretion of water does not, as compared with the excretion of urea, require that much work must be done by the kidneys This was demonstrated by the work of Barcroft and Straub

For practical purposes, to obtain the work done per gram of urea excreted, it will be noted from the formula that the specimen of urine need not be quantitatively collected since the work done per gram of urea excreted may be calculated from the logarithm of the factor Thus  $10.1 \times \text{Log}_{10} \text{ factor} = \text{Kilogram-meters work per gram urea excreted}$



# CASES OF MARKED HYPERTENSION, ADEQUATE RENAL FUNCTION AND NEURORETINITIS

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During the last three years a number of patients with hypertension and neuroretinitis have been referred from the Mayo Clinic to the medical service at the hospital with the diagnosis of chronic, diffuse, glomerular nephritis. In several of these, on further study, we found that the history and clinical findings differed from those usually found in cases of chronic nephritis, and also that the renal function was surprisingly good. The case reported here (Case 11) is an example of a group which seems to form a definite clinical type.

## REPORT OF CASE

CASE 11—A man, aged 45, sought medical advice at the Mayo Clinic because of severe headaches, general weakness, nervousness and loss of weight. Five years before, during treatment for dermatitis, his physician had noted increased blood pressure and albumin in the urine. Until one year before admission he had continued in good health, and had carried on his business successfully. At that time he began to have frequent occipital headaches which gradually increased in severity. Six months before, he had noticed that he was becoming nervous, he worried over minor details and could not sleep. From then until the physical examination he had lost 40 pounds (18 kg) in weight. During the last month his vision had occasionally been slightly blurred.

The patient seemed to be seriously ill, but aside from his blood pressure reading, 250 systolic and 190 diastolic, nothing alarming could be demonstrated. His heart was moderately enlarged, the peripheral vessels were definitely thickened, but there was no gross evidence of cardiac incompetency, such as pulmonary congestion or dependent edema. The mucous membranes were normal in appearance. Vision was impaired in one eye and normal in the other. The ophthalmoscope revealed severe neuroretinitis. Examination of the urine revealed the presence of a moderate amount of albumin and a few hyaline casts. The patient was kept under observation in the hospital for two weeks. There was no anemia, and slight, if any, disturbance of cardiac or renal function, nevertheless the nervousness, headache and insomnia continued and the retinitis did not improve. It seemed logical to believe that the disease was progressive and would soon lead to more serious symptoms, and this was confirmed by the patient's death five weeks after his dismissal from the hospital. Exact details of the last weeks of his illness were not obtainable, but a cerebral accident was probably the cause of death. The detailed findings in this and thirteen similar cases seem to differentiate them from chronic, diffuse, glomerular nephritis, and to justify their discussion as a group.

## SYMPTOMS AND PHYSICAL FINDINGS

The patients' ages varied from 24 to 49 years, the average being 39. The onset of symptoms before examination at the clinic varied from a few months to three years. Severe headache and other subjective or

objective nervous symptoms were at some time, or always present. There were evidences of serious cerebral involvement in eight of the fourteen cases. In four, there was hemiplegia or monoplegia. In four, convulsions occurred, in three of these, tumor of the cerebrum was suspected and considered, in one of which a subtemporal decompression was performed elsewhere with negative findings. Subjective disturbances of vision occurred in five cases, the symptoms varying from slight blurring sensations to almost complete blindness. In certain cases, the absence of visual disturbances with considerable retinal involvement, was striking. Loss of weight and strength occurred in half of the cases, the most marked loss of weight (75 pounds, 34 kg) occurring in the short period of six months. Symptoms of cardiac insufficiency, such as dyspnea and dependent edema, were not the rule, and when present, were minor in degree. Urinary symptoms were rarely complained of, and consisted of slight and moderate nocturia in half the cases. The urine had been examined previously in six cases, and albumin found in each, the history dating back in one case for eight years.

Although the patients were able to be up and about, they were all sent to the hospital for observation and for study periods, varying from one to seven weeks. Several were seen first in the Section on Ophthalmology because of eye symptoms, and when the retinal changes were found, a general examination was advised. A thorough physical examination was made, particular attention being given to the cardiovascular system. Clinical evidences of anemia were absent. Thickening of the brachial artery could always be demonstrated, the degree of change varying from a palpable thickening to tortuosity and beading. Examination of the heart by palpation and percussion revealed enlargement in twelve cases. The point of maximal impulse was outside the left mammary line. In some cases it could be felt in the axilla. In two cases, no cardiac enlargement was noted. The second heart sound was accentuated over the aortic area in thirteen of the cases. In the one case in which the second pulmonic sound was accentuated, there was an apical, systolic murmur with cardiac enlargement, so that the absence of a clicking, aortic second sound might well be due to a relative mitral insufficiency. Apical systolic murmurs were present in half the cases, and in five of these there was an associated aortic systolic murmur. No serious disturbance of the cardiac rhythm was observed. These cardiac findings are similar to those noted by Shaw<sup>1</sup> in his study of hyperpiesia.

At the time of examination the blood pressure was high. The maximal reading varied from 210 to 280 systolic and 140 to 190 diastolic.

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1 Shaw, H. B. *Hyperpiesia and Hyperpiesis*, London, Frowde, Hodder and Stoughton, 1922, p. 191.

TABLE 1—Clinical Findings

Case, Sex, and Age	Date	History of Present Illness	Physical Examination †	Blood Pressure				Retinal Changes	Electro- cardio- gram	Appearance of Nail Fold Capillaries	Result
				On Admission		At Dismissal					
				Sys- tole	Diastolic	Sys- tole	Diastolic				
1 ♀ 24	4/27/22	Tuberculous infection, right foot for twelve years, hypertension for seven years, headache and blurring vision for two months	Heart enlarged 1, aortic and apical systolic murmur, second aortic accentuated, peripheral sclerosis 2	280	190	210	140	Moderate arterio-sclerosis, well developed neuroretinitis	Normal	Moderate morphologic and functional changes	Death, 3/26/23
2 ♀ 45	8/26/21	Right hemiplegia six months, and vertigo, weakness, dyspnea and dimness of vision two months before, hypertension for six months, lost 75 pounds (34 kg.) in last six months	Heart enlarged 1, faint apical systolic murmur, second aortic accentuated, peripheral sclerosis 2	250		140		Moderate arterio-sclerosis, well developed neuroretinitis			Death, 8/31/21 cerebral hemorrhage, necropsy
3 ♂ 40	9/23/21	Periodic headaches for five years, severe for three, hypertension for one year, occasional edema of ankles at night	Heart enlarged 2, faint apical systolic murmur, second aortic accentuated, peripheral sclerosis 1 to 2	235	150	170	110	Moderate arterio-sclerosis, early neuroretinitis	Normal	Only slight changes	Death, January 1923
4 ♂ 25	10/24/21	Headache, loss of vision and loss of weight for twenty months, Jacksonian and grand mal attacks of epilepsy for fourteen months, hypertension for eighteen months, tumor cerebri?, subtemporal decompression 8/21/20	Heart not enlarged, systolic murmur over apex and aortic area, second aortic accentuated, peripheral sclerosis 1, bulging mass right temporal region	240	165	190	130	Marked arterio-sclerosis, secondary optic atrophy	Inverted T wave in Lead I	No striking abnormality	Death, 12/31/21
5 ♂ 40	12/21/20	Nocturnal one year, failing vision for seven months, progressive diminishing vision, two months, general convulsion while in hospital, tumor cerebri?	Heart enlarged 1, systolic murmur at apex and pulmonary area, second pulmonary accentuated, peripheral sclerosis 2 to 3	240	160	225	140	Moderate arterio-sclerosis, well developed neuroretinitis			Death, 1/29/21
6 ♂ 31	4/18/21	Headache and slight polyuria for from two to three years, impaired vision for six months epileptiform convulsions and hypertension, six weeks tumor cerebri?	Heart not enlarged, second aortic accentuated, peripheral sclerosis 1	260	160	225	155	Marked arterio-sclerosis, well developed neuroretinitis			Death, 7/8/21

7 ♂ 38	7/13/23	Headache, one year, loss of strength and weight (65 pounds, 29.5 kg), slight dyspnea and edema, four months before, blood pressure 250	Heart enlarged 2 to 3, systolic murmur at apex and aortic area, second aortic accentuated, peripheral sclerosis 2 to 3	255	155	230	140	Mild arteriosclerosis, well developed neuroretinitis	Inverted T-wave in Leads 1 and 2	Small constricted type	Death, 10/15/23
8 ♂ 45	3/15/23	Nocturnal oedipital headache for two years, lost 20 pounds (9 kg) in three months, hypertension for five weeks	Heart enlarged 1, second aortic accentuated, peripheral sclerosis 1	225	145	175	95	Marked arteriosclerosis, mild neuroretinitis	Normal		Condition satisfactory, 1/29/24
9 ♂ 40	11/6/23	Nocturnal headache for two years, severe with slight dyspnea for four months, hypertension for two years	Heart enlarged 1, second aortic accentuated, peripheral sclerosis 2	200	160	210	150	Moderate arteriosclerosis, well developed neuroretinitis			Condition satisfactory, 2/23/24
10 ♂ 45	11/8/23	Severe nocturnal headache and hypertension for two years, lost 40 pounds (18.1 kg) in one year	Heart enlarged 1, second aortic accentuated, peripheral sclerosis 2	200	120	210	150	Moderate arteriosclerosis, early neuroretinitis			Death, 2/8/24
11 ♂ 15	11/3/23	Oedipital headache for one year, hypertension for five years, insomnia, loss of weight and nervousness for seven months	Heart enlarged 1, second aortic markedly accentuated, peripheral sclerosis 2	250	190	190	115	Moderate arteriosclerosis, well developed neuroretinitis	Normal	Slight narrowing and tortuosity	Death, 12/25/23
12 ♂ 15	2/8/23	Headache for three years, severe for one year, loss of weight, 45 pounds (20.4 kg), hypertension for three months	Heart enlarged 1, second aortic accentuated, peripheral sclerosis 2	250	175	195	115	Marked arteriosclerosis, early neuroretinitis	Inverted T-wave in Leads 1 and 2		Death, 7/28/23
13 ♂ 47	11/24/22 11/15/23	Albumin and casts in urine for eight years, frontal headaches and occasional nocturia for six months, hypertension for one year, right hemiplegia two months before second admission	Heart enlarged 1, second aortic accentuated, peripheral sclerosis 1 to 2	220 180	140 130	180 180	120 120	Mild arteriosclerosis, mild neuroretinitis	Normal second admission	Nothing definitely abnormal	Condition satisfactory one year after first admission
14 ♂ 10	9/26/23	Migraine for years, severe headache, slight hemiplegia and hypertension for two years, severe headache, slight dyspnea and edema for two months	Heart enlarged 2, systolic murmur at apex and aortic area, second aortic accentuated, peripheral sclerosis 3	215	140	210	150	Evidences of hypertension, early neuroretinitis	Inverted T-wave in Leads 1 and 2		Death, 10/27/23

\* In this column, ♀ indicates female, ♂ male

† Grade 1 to 4 signifies variation from slight but definite change to most marked

Thirteen of the patients had known that they had hypertension. After several days of hospital treatment there was a fall in the pressure. The treatment consisted of periods of rest in bed, sedatives for insomnia and restlessness, hot baths and the periodic use of sodium nitrite. The blood pressure readings on dismissal from the hospital varied from 140 to 215 systolic, 80 to 140 diastolic (Table 1). Observations on the effect of repeated doses of sodium nitrite were made in seven cases. A temporary fall in blood pressure occurred, the systolic fall being more marked than the diastolic. The extent of the fall was considered an index of vasomotor response. The temporary effect of a hot bath on the hypertension was also noted. The fall in blood pressure was not usually so marked as after nitrite had been given (Table 2).

TABLE 2—*Effect of Sodium Nitrite and Hot Bath on Blood Pressure*

Case	Date	Blood Pressure							
		Sodium Nitrite, 0.03 Gm by Mouth Hourly for Six Consecutive Doses				Hot Bath Water at Temperature of From 95° to 110° F for From 10 to 20 Minutes			
		Before		1 Hour After Last Dose		Before		1 Hour After Bath	
		Sys tolic	Dias tolic	Sys tolic	Dias tolic	Sys tolic	Dias tolic	Sys tolic	Dias tolic
7	7/14/23	230	120	200*	110*				
	7/23/23					230	130	220	130
8	3/15/23	210	120	140	100				
9	11/ 4/23	230†	160	170	120				
	11/ 5/23					220	140	190	120
	11/21/23					210	140	215	135
10	11/18/23					200	145	190	130
11	11/ 4/23	210†	150	180	125				
	11/ 9/23					215	140	210	150
	11/13/23					220	150	205	150
12	2/ 9/23	210	100	150	90				
13	11/15/23	175	110	150	70				
	11/18/23					170	100	160	105
14	9/20/23	220	140	180	110				
	9/30/23					230	150	230	150
	10/ 1/23					230	150	210	130
	10/ 4/23	220	140	190	125				

\* Taken immediately following sixth dose of sodium nitrite

† 0.03 gm sodium nitrite given half hourly for six consecutive doses

In six cases, the nail fold capillaries were examined. In one case, they were definitely contracted, while in the others, no abnormalities, or only minor functional disturbances were observed.

In nine cases, electrocardiographic tracings were taken. Sinus rhythm was present in all, thus confirming the clinical observation that abnormal rhythms were not observed. In five cases the tracing did not reveal abnormalities, in four there were different degrees of T-wave negativity.

*Retinal Changes*—In all of the cases, ophthalmoscopic examination revealed neuroretinitis associated with retinal vascular changes (Table 3). In Case 14, there was no definite retinal arteriosclerosis,

TABLE 3—Retinal Findings

Case	Date	Hy- per- emia	Edema of Disks*	Right Left		Disks*	Edema of Disks	Cotton-wool Ex- udates	Snow bank Exu- dates	Papillary Retina	Idema of Peri-	Idema absorbing	Macular Star	Retinal Hemor- rhages	Peripheral Pig- ment Deposits	Retinal Detach- ment	Reduction in Cal- iber of Arteries	Irregularity in Cal- iber of Arteries	Exaggerated Arte- rial Reflex	Relative Enlarge- ment of Veins	Arteriovenous Compression	Perivasculitis	Choroidal sclerosis	Postneuritic Optic Atrophy	Vision		Moving objects	Counts fingers	Progression	No change Improvement	No change Improvement	Slight improvement	Improvement
																									Right	Left							
1	4/22/22	+	2	1																													
2	8/26/21		3	+																													
3	9/23/21																																
4	10/24/21	-																															
5	12/31/20		6	5																													
6	4/18/21		6	4																													
7	7/13/23	+	1-2	2																													
8	3/15/23																																
9	11/6/23	-	1	+																													
10	7/11/23	+	1	1																													
11	11/8/23	+	1	2																													
12	2/8/23																																
13	11/24/22		+	+																													
14	9/26/23	+		1																													

\* + signifies present, — not present

but there was exaggeration of the reflex stripe of the arteries, engorgement of the veins, and arteriovenous compression. In the other cases, there were varying degrees of arteriosclerosis of the hypertension type characterized by reduction and irregularity in caliber of the arteries. In Cases 4, 6, 9 and 11 perivascularitis was present, probably secondary to inflammation of the surrounding retina. In Cases 8 and 13, the neuroretinitis was of mild type, and was characterized by edema of the disc and retina, with scattered cotton wool exudates and hemorrhages, which tended to become fewer during the stay of the patients in the hospital.

In the other twelve patients, a severe and characteristic type of neuroretinitis was found. Cases 3, 10, 12 and 14 demonstrated what we regarded as an early stage of this retinitis. There were hyperemia and edema of the optic discs with swelling measurable from 1 to 2 diopters, edema of the peripapillary retina extending for varying distances toward the periphery, flame shaped and deep retinal hemorrhages, and cotton-wool exudates, or localized areas of increased density in the general edema. In Cases 1, 2, 5, 6, 7, 9 and 11, there was well developed neuroretinitis, which probably had been present for several weeks. The retinal picture was that of "albuminuric retinitis." The swelling of the discs varied from 1 to 6 diopters. Besides the edema of the retina, cotton-wool exudates and hemorrhages, there were scattered through the retina, especially between the disc and macula, bright white punctate exudates of the "absorbing-edema type." Peripherally, in regions from which the edema had subsided, there were small clumps of displaced pigment, often with a faint surrounding halo of choroidal atrophy. In Cases 5 and 6, the edema of the peripapillary retina was sufficiently dense to be described as "snow-bank." Partial or complete macular stars were present in Cases 1, 6 and 11. Localized retinal detachments occurred only in Case 5. In Case 4 there was postneuritic atrophy of the optic nerve, marked postinflammatory sclerosis of the retinal vessels, and atrophic and pigmentary changes in the retina and choroid. These we believed to be the end-results of a severe neuroretinitis of the type seen in the other cases, and reports of previous fundus examination by other oculists confirmed our opinion.

*Laboratory Findings*—The erythrocyte count and hemoglobin determinations confirmed the clinical observation that definite anemia was practically never present. In Case 5, the erythrocytes numbered 4,600,000 at one examination, the hemoglobin was 60 per cent, Dare, later it rose to 65 per cent. The erythrocytes occasionally numbered 4,000,000 on the patient's admission to the hospital, but when checked later, practically always rose. The leukocytes were determined in twelve cases. In ten of these, the count varied from 5,000 to 11,000, in one case it was 13,000. This patient developed a fatal cerebral hemorrhage

TABLE 4—Laboratory Findings

Blood										Urine						
Case	Date	Erythrocytes, Millions	Hemo globin, Cent (Dare)	Leuko cytes	Was-ser-mann Reac-tion	Urea, Mfg in Each 100 C c	Great-inin, Mfg in Each 100 C c	Uric Acid, Mfg in Each 100 C c (Folin and Wu)	Plasma Chlorids, Mfg in Each 100 C c	Specific Gravity			Phenol- Chlorid Test, % sulphone Concentrations			Sodium Benzoate After Excre-tion, 3 Hours C c
										Varia-tion	With Concen-tration Test	Water Test	Excretion, 2 Hours, per Cent	Before Injec-tion	After Injec-tion	
1	4/27/22	4 60	76	7,000	—	18				1 009-1 021		1 3	0	45		
2	5/17/22		111*		—	15				1 006-1 026	1 006	1	Occasional			905
3	8/26/21	5 10	82	13,000	—	34	1 9	3 1		1 001-1 027	1 027	1-3	1 3	60		1,145
	9/23/21		76	10,700	—	29	1 6	4 0								
	10/27/21					41	1 5	3 8								
	10/31/21	4 60	76	8,400		51	1 6	3 8								
	11/14/21					21	1 6	2 8						50		
	2/10/22	4 50	75	8,400		38	1 4	3 9		1 004-1 028	1 028					
4	10/24/21	4 70	78	6,400	—	27	1 4	3 6		1 006-1 034	1 034	1	Occasional	45		1,540
5	12/31/20	4 60	60	20,000	—	34	1 6	1 9		1 004-1 016		1 3	1 3	65		
	1/11/21	4 25	65	12,000		42	1 6	2 9						40		
6	4/21/21	4 46	74	8,200	—	46	1 5	3 4	590	1 003-1 030	1 027	1-2	1 2	70		1,030
	4/29/21					35	1 5	2 7	600							
7	7/13/21	4 00	114*	6,700	—	29	1 8	4 0†		1 001-1 036	1 030	1 2		40		
8	3/12/23	4 70	76	5,000	—	22	1 7	3 7†		1 002-1 027	1 027	0 1	1	65	0 8	1 4
	3/15/23		78-100*			32									87% normal	1,110
9	11/ 6/23		127*		—	37	2 3	5 1†		1 003-1 026						
	11/14/23	5 35	92	8,800	—	41	2 4	5 7†				1-2	1 3	45	1 3	3 2
10	11/ 8/23	4 10	75	7,200	—	32	2 2	4 8†		1 007-1 020	1 020	1 2	1	30	0 3	0 2
	11/15/23													30		
11	11/ 3/23	4 60	75	9,000	—	34	2 0	4 4†								
	11/ 6/23	4 50	81		—	31	2 0	4 4†	575	1 001-1 020	1 020	1 2	1	45	0 7	1 5
12	2/ 8/23	4 90	79-103*	4,700	—	55	2 7	4 5†	595	1 009-1 015	1 014	1-2	1	35	0 3	0 1
	2/19/23		95*			25	2 4	3 3†								
	2/19/23					32	1 7	3 2†		1 001-1 031	1 028	0-1	0-1	55		1,030
13	11/24/22	4 60	76-119*	6 000	—	22	1 7	2 4†	570	1 002-1 027	1 027	0-1	0	40	0 7	2 3
	11/15/23		118*			29	2 3	3 6†		1 005-1 025	1 025	1 2	1	55		1,005
14	9/26/23		118*		—											1,025

\* Haldane-Palmer carbon monoxid, or Osgood acid hematin methods

† Folin new method described in J Biol Chem 54 153, 1922

‡ Albumin and casts have been graded from 1 to 4. One equals smallest amount or number, 4 the largest

§ Normal chlorid per cent concentration, before injection of from 0 8 to 1 9, after injection of from 1 8 to 2 0



within a few days. In Case 5, the leukocyte count was 20,000. The cause of this temporary leukocytosis was not determined. In thirteen cases, the Wassermann reaction in the blood was negative. In two of these, it was also negative in the spinal fluid. It is of interest that there was no history or physical findings suggestive of syphilitic infection in any of these cases (Table 4).

*Urinary Findings*—Albumin, casts, and a few erythrocytes and leukocytes were found at one or more examinations in each case. The amount of albumin varied markedly even in the same case. In three cases, a heavy precipitate was occasionally found. In only four cases was the number of hyaline and granular casts at any time numerous. Cellular casts, actual pyuria or hematuria were not observed.

Normally, the specific gravity of the urine varies between 1.003 and 1.030. In six of the cases in this series the variation was approximately normal. In four, the variation was slightly decreased, although the optimal conditions for concentration and dilution were not obtained. The drinking of a large amount of water was found to aggravate the nervous symptoms of certain of these patients so that the test was sometimes omitted. On the other hand, certain patients found the dry diet unpalatable. Under satisfactory conditions, three patients were unable to excrete a concentrated urine. The maximal specific gravity never rose above 1.020.

*Water Excretion*—The water test was satisfactorily carried out in seven cases. In one, Case 2, the specific gravity of the urine failed to fall to 1.003. In four cases, the total urine output was normal or slightly reduced, with the curve of excretion and fall in specific gravity within the normal limits. In two, the urine output was reduced, while in one the curve of excretion was abnormal.

The phenolsulphonephthalein excretion was determined in thirteen cases. In seven, the output, at least on one occasion, was 50 per cent or higher, in four, from 40 to 45 per cent, while in two, it was from 30 to 35 per cent. In the latter two cases, total renal function was distinctly impaired. In six cases, 5 gm. of sodium chlorid was injected intravenously, according to the technic instituted by Barrier and Whelan<sup>2</sup>. In four cases, the excretion was normal or slightly reduced, while in two, it was abnormally decreased. The sodium benzoate test of Kingsbury<sup>3</sup> was carried out in a single case (Case 8), and a normal result obtained.

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<sup>2</sup> Barrier, C. W., and Whelan, Mary. Personal communication.

<sup>3</sup> Kingsbury, F. B., and Swanson, W. W. The Synthesis and Elimination of Hippuric Acid in Nephritis. A New Renal Function Test, *Arch. Int. Med.* 28: 220-236 (Aug.) 1921.

## CHEMICAL STUDIES OF THE BLOOD

The urea content of whole blood was normal in eight cases, ranging from 15 to 34 mg for each 100 c c. In three cases the values bordered on the abnormal, varying from 35 to 42 mg. There was a distinct increase above the normal in the three remaining cases, the amount varying from 46 to 55 mg. The patient, Case 3, was under observation in the hospital for a period of seven weeks, and for one of two weeks. During the first period, the blood urea was determined at weekly intervals, in five instances the amount was below 31 mg, while in two, it was 41 and 51 mg. At the time of the two latter determinations, there were no other evidences of definite renal insufficiency. These findings indicate that fluctuations in the urea content of the blood may occur in this type of renal injury, but even under such severe testing, the amount does not reach the level so commonly observed in cases of chronic, diffuse, glomerular nephritis. In only one of three cases (Case 12) in which the values were from 46 to 55 mg was the renal function distinctly impaired.

The creatinin content of whole blood was determined in thirteen cases, and in only four was it above 2.0 mg for each 100 c c. The increased values varied from 2.2 to 2.7 mg and in three, including Case 12, there was an associated increased blood urea.

Estimations of the uric acid concentration in the whole blood were made in twelve cases. The findings in five were within normal limits, in the seven remaining cases, the abnormal increase was never striking in amount and not necessarily associated with measurable impairment of renal function.

The chlorid content of the plasma was determined in six cases. In only one, Case 9, was the amount abnormally increased, amounting to 665 mg for each 100 c c. In this case, there was no visible edema or inability to excrete sodium chlorid, although extra water was not satisfactorily eliminated.

## PATHOLOGIC FINDINGS

Only one patient of this series (Case 2) died while under observation. Cerebral symptoms associated with left-sided weakness developed suddenly, and in a few hours the patient lapsed into deep coma and died forty-eight hours later.

*Necropsy Findings*—Bilateral cerebral hemorrhage, marked cardiac hypertrophy, moderate generalized arteriosclerosis, arteriosclerotic change of the kidneys and terminal bronchopneumonia were noted. On sectioning the brain, both ventricles were found filled with blood, the amount of blood being greater in the left. The heart weighed 400 gm and there was marked hypertrophy of the left ventricle. Scattered throughout the coronaries were small yellowish areas of

thickening, but the lumen was patent throughout. The kidneys weighed 135 gm each. The capsule was adherent, and when stripped revealed a fine granular surface. On section, the cut surfaces showed some pale areas and in the pelves of both kidneys there were discrete punctate areas of hemorrhage.

There were numerous focal areas of increase of the interstitial connective tissue in the cortex. In the intervening portions, the glomeruli were often considerably increased in size, some of them fully twice the size of a normal glomerulus. The glomeruli showed occasional thickening of the capsules and lobulation and partial hyalinization of the tufts with an irregularity in the form of the capsule itself. Occasionally a glomerulus was completely obliterated.

The arteries showed distinct thickening of the intima and the inner portion of the media, with hyalinization. Calcareous particles were seen in the medullary portions adjacent to the tubules. The tubular epithelium was in fairly good condition. The lumina of the tubules were occasionally dilated and there were a few cysts. An occasional hyaline cast was seen in the limbs of Henle's loops. A microscopic diagnosis of moderate renal arteriosclerosis was made.

Eleven other patients are known to have died since they were observed in the clinic, but no accurate data on the immediate cause could be obtained.

#### COMMENT

Volhard and Fahr<sup>4</sup> have used the term "malignant hypertension" to indicate those cases of vascular sclerosis which later develop definite renal insufficiency. On the other hand, we have limited the term to those cases of severe, diffuse, vascular disease which do not show distinct renal insufficiency. The term "malignant" is applicable to these cases because of the frequent loss of weight, cerebral symptoms and accidents, continued high blood pressure, severe neuroretinitis and the serious prognosis. The age incidence, history, clinical and laboratory findings are similar to those in the severe cases of so-called essential hypertension or hyperpiesia described by Allbutt<sup>5</sup>. The persistent hypertension, cardiac enlargement, peripheral sclerosis, retinal changes, absence of anemia, and only moderate or no reduction in renal function seem to constitute a distinct clinical entity.

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<sup>4</sup> Volhard, F, and Fahr, K. T. *Die brightsche Nierenkrankheit*, Klinik, Pathologie, und Atlas, Berlin, Julius Springer, 1914, p. 300.

<sup>5</sup> Allbutt, C. *Senile Plethora, or High Arterial Pressure in Elderly Persons*, Tr. Hunterian Soc., 1895-1896, pp. 38-57 (quoted in *Diseases of the Arteries, Including Angina Pectoris*, New York, The Macmillan Company, 1910, 1915), *An Address on Arteriosclerosis and the Kidneys*, Brit. M. J. 1 853, 922-936, 1911.

Volhard and Fahr,<sup>4</sup> Shaw,<sup>1</sup> and Ellis and Marrack<sup>6</sup> have pointed out several features differentiating these cases from chronic glomerular nephritis, namely, higher blood pressure, absence of anemia, adequate renal function, and absence of extensive diffuse lesions in the kidneys at necropsy. Taking this series of cases as a whole, disturbances of renal function, when present, were never severe. In certain cases there was no abnormality except a trace of albumin and a few casts, in others diminished excretion of water, chlorids, and phenolsulphone-phthalein were noted, but not enough to derange general metabolism, or produce abnormal symptoms. Analyses of the blood in the majority of cases revealed no evidence of nitrogen retention. When it was present, the increase above normal was so slight that it could not be termed azotemia. We believe that, besides the foregoing differences, the severe hemorrhagic and exudative neuroretinitis, while "albuminuric" in type, has certain distinctive features. Chief among these are the presence of definite retinal arteriosclerosis of the hypertension type and the absence of anemia. Retinal edema is usually not so extensive and less often assumes the "snow-bank" type, and macular stars are less common than in the nephritic cases. Behan<sup>7</sup> has mentioned the occurrence of neuroretinitis in patients with high blood pressure without renal insufficiency. In a series of papers, Benedict<sup>8</sup> has called attention to the effect of hypertension on the retinal vessels, and to the influence of vascular changes and toxemia in the production of retinitis in cardiovascular renal disease. He cited several cases in which the renal function was good at the time of examination. In some of these he suggested the possibility of a transitory preceding or subsequent renal insufficiency.

The diagnosis of cerebral tumor was seriously considered in three cases. That cerebral tumor and malignant hypertension may have been present in the same patient is quite possible, but as necropsies were not performed, the diagnosis of tumor could not be made. In Case 4, an exploratory craniotomy failed to reveal a tumor. On the other hand, Hench<sup>9</sup> has found that hypertension rarely occurs in undoubted

6 Ellis, A. W. M., and Marrack, J. R. An Investigation of Renal Function in Patients with Retinitis and High Blood Pressure, *Lancet* **1** 891-893 (May 5) 1923.

7 Behan, J. L. The Fundus Changes in Nephritis, *J. A. M. A.* **78** 1691-1694 (June 3) 1922.

8 Benedict, W. L. Retinitis Associated with Disease of the Cardiovascular System, *New York M. J.* **117** 741-745 (June 20) 1923.

9 Dr. P. S. Hench investigated the blood pressure findings in a group of forty-four patients with brain tumors in the clinic. The tumor was actually demonstrated at operation or necropsy or at both examinations. The age incidence was from 20 to 51 years. Only two patients had a systolic blood pressure of over 150. In one, a woman, aged 51, the blood pressure on admission was 186 systolic and 120 diastolic, and nine days later was 150 systolic and 90 diastolic. There was evidence of sclerosis in the retinal arteries. The second case was a man, aged 43. The blood pressure was 152 systolic and 100 diastolic with no evidence of arteriosclerosis.

cases of brain tumor. Thus the high blood pressure and certain differential points in the retinal findings, particularly the presence of arteriosclerosis and the distribution of the edema, lead us to believe that the symptoms suggesting cerebral tumor are secondary to the hypertensive vascular condition.

The prognosis in twelve of these cases was extremely serious. Eleven patients died within from a week to fifteen months of their initial examination in the clinic. The remaining patient left the hospital November, 1923, and he is still able to do his work though his headaches are persistent and severe.

In Cases 8 and 13 the hypertension on admission to the hospital was not so marked and responded readily to rest and hospital treatment. The general arteriosclerosis and cardiac enlargement were moderate in degree, the neuroretinitis was mild, and renal functional studies revealed normal excretion. The patients improved and have enjoyed a restricted, but comfortable existence since they were dismissed from observation one year ago. The milder neuroretinitis found in these two cases is of less serious local and general import than the characteristic severe type. Vision was not affected and definite improvement occurred while the patient was under treatment. In such a retinitis, the lesion may disappear completely without residuals. These findings suggest that there are border line conditions, in which it is impossible to make a differential diagnosis between cases of early malignant and essential hypertension. In order to make the distinction, accurate observation during the subsequent courses of the disease appears to be necessary.

The determining local factor in the production of the severe retinitis is not known. It does not seem to depend on azotemia, as suggested by Opin and Rochon-Duvigneaud<sup>10</sup> and Leber,<sup>11</sup> nor on the severity of the preceding sclerosis in the retinal arteries, but may be associated, as Leber, and Volhard<sup>12</sup> and Schieck<sup>13</sup> suggest, with marked contraction in the smaller vessels. Its course is chronic and, once initiated, seems to be little influenced by local or general treatment. During its active stage, its effect on vision seems to depend on the amount of edema present in the macular region. In the majority of cases, vision is surprisingly good. If the patient lives long enough, the retinitis will

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10 Opin and Rochon-Duvigneaud. *Lesions comparees de la retine et des autres organes chez les malades atteints de retinite brightique, indications qu'elles fournissent sur la pathogenie de l'affection*, Arch. d'ophth. **24** 155-176, 1904.

11 Leber, T. *Die Netzhauterkrankungen bei Nierenleiden*, Graefe-Saemisch Handb. d. ges. Augenheilk. **7** 913-926, 1915.

12 Volhard, F. *Die doppelseitigen hamatogenen Nierenerkrankungen*, Berlin, Julius Springer, 1918, p. 576.

13 Schieck, F., and Volhard, F. *Netzhautveränderungen und Nierenleiden*, Zentralbl. f. d. ges. Ophthal. u. Grenzgeb. **5** 465-481, 1921.

probably heal ultimately, the end-results being varying degrees of post-neuritic optic nerve and retinal atrophy with corresponding slight or great loss of vision

The results obtained in this study indicate that the finding of a serious neuroretinitis in cases of marked hypertension is of great prognostic significance. The ophthalmoscopic picture may be the earliest sign of the conversion of an essential into a malignant hypertension, and thus reveal a serious general vascular lesion when cardiac and renal function is surprisingly adequate. In such cases, it seems more reasonable to assume that the retinitis is dependent on the hypertensive vascular disease, rather than on a primary lesion of the kidney.

#### SUMMARY

Certain patients with severe neuroretinitis show little or no evidence of renal insufficiency. They have marked hypertension, moderate peripheral arteriosclerosis and cardiac hypertrophy, but their condition differs definitely from those with chronic diffuse glomerular nephritis. From the history, clinical and laboratory findings, and subsequent course, these patients appear to constitute a distinct clinical group.

# THE METABOLISM OF GALACTOSE

## I THE THRESHOLD OF TOLERANCE IN NORMAL ADULTS \*

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### INTRODUCTION

This paper deals with certain of the results of a study, begun in 1916, on the diagnosis of certain endocrine disorders. The compilation of the data has been greatly delayed, but within the last two years, however, it has been possible to prosecute the studies actively, and this report embodies a small completed portion of the whole investigation. In evaluating the mass of data resulting from earlier animal experimentation, it was felt that the greatest caution was imperative in translating it into terms of human experience. By confining the studies to man, one major cause of uncertainty has been eliminated. While this has imposed certain limitations, the direct applicability of the results has brought ample compensation.

### REASONS FOR SELECTION OF CARBOHYDRATE METABOLISM AS BASIS OF STUDY

With the selection of the subjects for experiment, the natural sequel was the determination of the tests to be applied. The field of so-called vital function testing offers a wealth of suggestions. With the great majority, if not with all, however, the goal has been to secure a test which should be sharply indicative of a single condition or of deviation in an individual functional capacity. With an apparently complex control of all bodily functions, this method of approach has led to the observation of numerous exceptions in the individual cases which have cast grave doubts on the specific validity of the test, and thus inhibited further investigation. If approached from the opposite point of view, however, those tests in which the largest number of factors may be operative offer the most attractive field of study. By the judicious selection of a variety of such measurements and the application of them, first to normal subjects and then to subjects in whom there existed some well defined, sharply characterized pathologic changes, the several variations produced by dysfunction might be ascertained, both in sense and in magnitude. Even granting a manifold and interdependent control of a given capacity, it seemed hardly probable that a series of widely

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\* Presented at the Seventeenth Annual Meeting of the American Society of Biological Chemists, Toronto, Dec 29, 1922

divergent tests should be under the same detailed and quantitative regulation. Thus, by establishing normal criteria, and by noting the influence exercised by well defined variations from the norm, it was hoped that sufficient data might be obtained to offer a basis for differential diagnosis. Further, a normal response to a given test produced by two opposing and mutually compensatory influences could hardly be produced throughout a series of tests, and so would be equally informative with wide divergences from the established normal.

It is hardly necessary to add that all tests must be quantitative, must be performed under rigidly controlled conditions, and that every precaution is observed to attain the highest degree of accuracy.

Assuming this point of view, the carbohydrate metabolism becomes a potentially most productive field for investigation. For several decades it has been recognized that the human body has a very definite limit to the amount of carbohydrate that can be metabolized under certain definitely circumscribed conditions, the so-called threshold of tolerance, and that there are numerous agencies which could affect this amount, either increasing or diminishing it.

Aside from the dominant influence of the internal secretions of the pancreas, severally, the liver, kidneys, the entire endocrine system and the central nervous system may or do all play some part. Further, aside from organic control, such factors as degree of muscular activity, temperature, nutrition and fatigue, have been reported as exercising influence, and, finally, certain states such as pregnancy, fever and neuroses of traumatic origin are also to be reckoned with. As the body receptivity varies with the several carbohydrates, it becomes necessary to designate the particular sugar which shall form the basis of the test.

#### CHOICE OF SUGAR

In the first place, the choice is directly limited to the hexose sugars. The adoption of disaccharids or polysaccharids is interdicted as introducing one more element of complication in a problem already far from simple. Of the several modes of administration, the oral route possesses several manifest advantages. Intraperitoneal and subcutaneous administration can be eliminated at once, rectal feeding represents a last resort rather than a method of election, and the intravenous technic of Wood-yatt<sup>1</sup> and his co-workers, ingenious and highly interesting though it is, offers on the one hand certain obvious difficulties, and on the other, fails to throw light on certain of the physiologic functions which it was desired to study. With the field thus limited, the problem of selection

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<sup>1</sup> Wodyatt, R. T., Sansum, N. D., and Wilder, R. M. Prolonged and Accurately Timed Intravenous Injections of Sugar, *J. A. M. A.* **65**: 2067 (Dec. 11) 1915.



is greatly simplified. Many of the conditions to be studied were reported in the literature as having greatly increased so-called tolerance thresholds. A few preliminary experiments demonstrated that with the large doses of glucose and of fructose, which many of the subjects would require, the digestive disturbances excited by test meals of heroic size would inevitably eliminate an appreciable number of observations. True, Miura<sup>2</sup> had exhibited massive doses of several carbohydrates with some measure of success, but personal experience showed the outcome to be highly precarious. Of the available sugars, then, only galactose remained.<sup>3</sup> This sugar, studied with others by several of the earlier students of carbohydrate metabolism, first attained the dignity of an independent diagnostic entity when suggested by Bauer<sup>4</sup> in 1906 as a test for liver function. A series of articles followed, chiefly clinical in character, in which the utility of galactose as a test meal was thoroughly canvassed.

From the mass of conflicting data one fact stood out saliently, namely, that the exciting dose of galactose was too small to cause the digestive disturbances which so marred the utility of the more common fructose and glucose. Further, galactose is not a foreign sugar in the sense that it forms no part of normal nutrition. Conjugated with glucose, it is the basis of carbohydrate metabolism of our earlier years, and is present in appreciable amounts in the diet of maturity.

The galactose assimilation in young children is of much interest in this connection. Excluding studies in which the presence of another sugar constitutes a disturbing element, several groups of feeding experiments are recorded. Schirokauer<sup>5</sup> with normal and lymphatic children, aged from 2 to 4 years, and Stern<sup>6</sup> with children aged from 4 to 8, all found results approximating adult levels. A most complete study is given in the work of Meyer and Stern,<sup>7</sup> who, with children ranging from 3 months to 7½ years of age, and with doses of galactose of from 10 to 60 gm. carried out a series of well devised and carefully controlled observations. The results show assimilation limits which are definitely comparable with those observed in the adult.

That galactose can build glycogen would seem to be the consensus of opinion. Brasch,<sup>8</sup> in a most interesting study of carbohydrate utilization, gives a very good review of the earlier literature. Perfusion

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2 Miura *Ztschr f Biol* **32** 281, 1895

3 The pentoses were of too doubtful a purity, too expensive and, in the main, too foreign to normal human metabolism to be taken in consideration.

4 Bauer *Wien Med Wchnschr* **56** 2537, 1906

5 Schirokauer *Jarhrb f Kinderh* **79** 581, 1914

6 Stern *Med Klin* **15** 873, 1919

7 Meyer and Stern *Arch f Kinderh* **68** 241

8 Brasch *Ztschr f Biol* **50** 112, 1907

experiments by Grube<sup>9</sup> with tortoise livers and McGuigan<sup>10</sup> with muscle preparations show direct utilization Roubitschek<sup>11</sup> and Hurwitz and Bloomfield<sup>12</sup> who using lactose in experiments with animals poisoned with phosphorus and chloroform respectively, conclude that galactose is a former of glycogen Most recently Mann and Magath<sup>13</sup> have shown that the revivifying effect of glucose on dogs dying after liver extirpation, is duplicated in small measure by galactose

Galactose, then, as a sugar not entirely foreign to the human economy, with so low an assimilation limit as to preclude nullifying digestive disturbance, of well defined chemical and physical properties, and apparently capable of direct absorption, was felt to be the most desirable of available carbohydrates The results obtained with it have warranted amply the original selection

#### THE "THRESHOLD OF TOLERANCE"

The significance and exact meaning of the term, "Threshold of Tolerance," require further discussion Used as it is freely in contemporary literature to indicate two diverse, and, as I believe, mutually independent phenomena, definition must be made if grave confusion is to be avoided

#### DEFINITION OF "TOLERANCE THRESHOLD"

The terms "threshold of tolerance," has been applied severally to the following conditions.

1 The maximum amount of carbohydrate, and later, as the sugar-forming properties of other foods were recognized, the total food intake, which could be ingested by a sugar-free diabetic patient without causing a glycosuria

2 The amount of a carbohydrate given under various conditions of control, which would excite a transitory but detectable melituria the so-called assimilation limit

3 The amount of carbohydrate which would produce an hyperglycemia just below the level of the so-called renal threshold

In the first two, at least, the interpretation of a positive response has varied from the detection of the merest trace to the elimination of a definite number of grams Since Jacobsen's<sup>14</sup> paper in 1913 gave a concrete magnitude to the term, "renal threshold," and particularly

9 Grube Arch f d ges Physiol **118** 1, 1907

10 McGuigan Am J Physiol **21**:334, 1908

11 Roubitschek Deutsch Arch f klin Med **108**:225, 1912

12 Hurwitz and Bloomfield Bull Johns Hopkins Hosp **24**:380, 1913

13 Mann, F C, and Magath, T B Studies on the Physiology of the Liver, Arch Int. Med **30** 171 (Aug) 1922

14 Jacobsen Biochem Ztschr **56**:471 1913

through the development of blood analytic methods, the blood picture, with the urine findings as a by no means necessary complement, has become the goal of investigation. In the present paper only the concept will be discussed which deals with the provocation of a melituria by an ingested sugar, and that sugar galactose. A preliminary survey of the literature gives meager assistance in determining the assimilation limit for the sugar in question. The more significant literature can be assembled in tabular form for purposes of discussion. Dealing first with so-called adult normal patients, in this instance cases without liver involvement, the data are found in Table 1. The results are somewhat

TABLE 1—*Normal Patients Liver and Thyroid Cases and Neuroses Omitted*

Author	Year	Dose	Number	+	—	Per Cent
Bauer <sup>16</sup>	1912	40	60	7 <sup>4</sup>	53	12
Reiss and Jehn <sup>31</sup>	1912	40	12	1 <sup>3</sup>	11	8
Hatiegan Wien klin Wchnschr 27. 358, 1914	1914	40	4	0 <sup>1</sup>	4	0
Maliwa <sup>15</sup>	1914	40	21	20 <sup>1</sup>	1	95
Wagner <sup>29</sup>	1914	40	26	7 <sup>2</sup>	19	27
Worner and Reiss Deutsch med Wchn schr 40 907, 1914	1914	40	9	0 <sup>4</sup>	9	0
Stern <sup>6</sup>	1919	40	6	5 <sup>1</sup>	1	83
			138	40	98	29
Strauss <sup>20</sup>	1913	30	22	2 <sup>1</sup>	20	9
Uhlmann <sup>17</sup>	1915	30	25	20 <sup>1</sup>	5	80
			47	22	25	47
Frey Ztschr f klin Med 72 383, 1911	1911	20	8	4 <sup>1</sup>	4	50

1 Qualitative test

2 &gt; 1 gram

3 &gt; 2 grams

4 &gt; 3 grams

diverse. Maliwa,<sup>15</sup> using a qualitative test as his criterion, finds 95 per cent of his cases positive with 40 gm while Bauer,<sup>16</sup> regarding a melituria of less than 3 gm as of no significance, reports but 12 per cent positive to the test.

Under apparently similar conditions, Stern<sup>6</sup> and Uhlmann<sup>17</sup> secured diametrically opposite results.

Many more data are available, but as they offer no better solution of the problem, in the interest of brevity extended discussion may be omitted.

Briefly summarized, it would seem as if the limits lay somewhere between 20 and 50 gm, with the middle figures of from 30 to 40 being the more probable. Von Noorden<sup>18</sup> places the so-called tolerance threshold at 20 gm for orally administered galactose. Hirose,<sup>19</sup> in an

15 Maliwa Med Klin 10 762, 1914

16 Bauer Berl klin Wchnschr 49 1498, 1912

17 Uhlmann Arch f Verdauungskr 21 353, 1915

18 von Noorden Die Zuckerkrankheit, Berlin, Hirschwald, 1910

19 Hirose Deutsch med Wchnschr 38 1414, 1912

excellently conceived and executed investigation, adopts 25, Strauss<sup>20</sup> prefers 30 as the most probable normal figure, and a group of investigators select 40 as the best available figure. The values found by Meyer and Stern<sup>7</sup> for young children, already quoted, are particularly significant in demonstrating the relative independence of the so-called threshold of age.

The criterion for a positive response is highly important, and in the earlier work showed pleasing variety. The apparent failure to recognize the significance of the carbohydrate paradox (Allen<sup>21</sup>) invalidates the significance of much of the published data. The appearance of detectable reducing material in an otherwise apparently sugar-free urine would seem to me to be a certain basis on which to gauge results. True, it establishes as the criterion the sensitivity of some qualitative chemical reagent. Further, numerous writers on this topic have treated the presence of "mere traces of urine sugar" in a very cavalier manner, and denied them all significance.

But the demonstration of detectable amounts of reducing substance after the administration of carbohydrate test meals in urines, otherwise uniformly negative to the test applied, indicates definitely that some change has taken place which can be referred only to one exciting cause. And with the selection of a reagent of proved sensitivity, reliability, and uniformity of behavior, a sound basis for comparison is established.

Some years ago, Benedict, Osterberg and Neuwirth<sup>22</sup> demonstrated the fact that there is a continuous leakage through the kidneys of some reducing substance or substances, and that the ingestion of any food caused an increase in the amount. That the urine always contained minute amounts of "sugar," had been recognized long before, but the authors in question gave a quantitative expression to the phenomenon which was most convincing. Further, they applied the term "glycuresis" to the increase in urine sugar resulting from ingestion of food substances in substitution for the more common, and possibly misleading "glycosuria."

More recently, a very comprehensive study of certain phases of carbohydrate metabolism by Folin and Berglund<sup>23</sup> has appeared, in which a most interesting and suggestive explanation is offered. As the results of their experiments, the authors conclude that "glycuresis represents the absorption and excretion of foreign, unusable carbohydrate

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20 Strauss. *Neurol Centralbl* **32** 1281, 1913, *Deutsch med Wchnschr* **39** 1780, 1913.

21 Allen. *Glycosuria and Diabetes*, 1913.

22 Benedict, S. R., Osterberg, E., and Neuwirth, I. *J Biol Chem* **35** 217 (Aug) 1918. Benedict, S. R., and Osterberg, E. *J Biol Chem* **55** 769 (April) 1923.

23 Folin, O., and Berglund, H. *J Biol Chem* **51** 213 (March) 1922.

materials " and that the "sugar of normal urine is a motley variety of carbohydrate products and derivatives" Benedict,<sup>24</sup> in a later paper contests this interpretation and reiterates his belief in the absence of any absolute tolerance for glucose in the individual. This belief has also been expressed recently by Rosenberg,<sup>25</sup> and is indeed shared by Folin and Berglund with regard to galactose and lactose, but not for glucose and fructose.

On the other hand, Benedict is of the opinion that certainly not more than 50 per cent, and usually not over 25 per cent of urine sugar is glucose, an opinion also voiced by Maclean<sup>26</sup> as early as 1907. The work of Oppler<sup>27</sup> might be cited in this connection. This investigator finds in normal urine some 0.04 per cent of a reducing, fermentable substance which is, however, optically inactive. He further concludes that glucose constitutes but a small part (about 25 per cent) of the whole. Without citing further instances from the literature, it may seem to be fairly obvious that whatever individual differences of opinion may exist, all are agreed that a part, at least, of the reducing material is not glucose. The stress laid by Benedict on fermentable and nonfermentable moieties in the urine does not seem to me to be of such paramount importance as, on the one hand, other carbohydrates than glucose undergo this process, while on the other, there is always the possibility of the yeast introducing materials of a reducing nature which would still further cloud the issue. Another thought expressed by Benedict introduces the stereomeric relationships of  $\alpha$  and  $\beta$  modifications of a given sugar, and reference is made to the recent work of Winter and Smith<sup>28</sup>. The drastic treatment to which these latter authors subjected their material may arouse some question of an extraneous and superimposed chemical effect. Even so, the lability of the simple carbohydrate molecule, the existence of the *gamma* modification, give food for thought in connection with the present problem.

After relatively large doses of galactose, several writers have identified galactose in the urine. Among others, Bauer<sup>4</sup> and Wagner<sup>29</sup> use mucic acid as a means of quantitating the output, yet most recently Bodansky,<sup>30</sup> working with dogs, was rarely able to detect galactose as such, although many grams of reducing material were present in the urine. The choice of his subjects may have some bearing on this apparent contradiction. Fortified by the positive mucic acid and osazone

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24 Benedict, S. R. The Detection and Estimation of Glucose in Urine, *J. A. M. A.* **57** 1193 (Oct 7) 1911.

25 Rosenberg. *Arch. f. exper. Path. u. Pharmacol.* **93** 208, 1922.

26 Maclean. *J. Biol. Chem.* **2** 431, 1907.

27 Oppler. *Ztschr. f. Physiol. Chem.* **75** 71, 1911.

28 Winter, L. B., and Smith, W. *J. Physiol.* **57** 101 (Dec.) 1922.

29 Wagner. *Ztschr. klin. Med.* **80** 174, 1914.

30 Bodansky, M. *J. Biol. Chem.* **56** 387 (June) 1923.

(Reiss and Jehn<sup>31</sup>) findings of other observers, I have applied the Tollens test (phloroglucinol-hydrochloric acid) with uniformly positive results where reducing material was shown to be present by a sensitive copper reduction test (Benedict's)

To summarize the foregoing, the so-called "normal sugar" of the urine is generally regarded as containing but small amounts of glucose, if indeed there is any. Ingestion of appreciable amounts of the common sugars may show small increases in this "glycuresis," or better, "melituresis," the addition of other food stimulates a larger excretion, but in all instances the amounts are absolutely small. With the ingestion of certain larger quantities of sugar, the amounts severally dependent on the character of the sugar, the conditions of administration, and the metabolic relation of the subject, there is at once a notable increase in the amount of the "sugar" elimination. It becomes qualitatively detectable in the urine, and a part, at least, of the reducing body thus appearing, is identical with that which was ingested. Further, the ingestion of slightly smaller amounts fails to produce any of the above phenomena.

It would certainly seem here as if there was some definite transition, an inauguration of new, rather than a quantitative increase of old processes. The Folin-Berglund interpretation of the character of urinary "normal sugar," and of the definite but small increases observed under the stimulus of food or sub-tolerance doses of carbohydrate, would seem to give a most workable explanation of the whole mechanism under discussion.

When one considers the extreme difficulty of freeing such stable compounds as inorganic salts from the least trace of impurity, the impossibility of purifying such labile substances as the carbohydrates from contaminants is patent. A procedure of sufficient drasticity to remove one offending material may well give rise to yet larger quantities of another.

For purposes of convenience, then and with full recognition of the incompleteness of the experimental background for certain assumptions made, in the following discussion certain conventions will be adopted.

First, the term "super tolerance dose" will be used to designate that amount of galactose, which, administered to an adult in basal condition (i. e., resting and fasting) in water, in a concentration of from 10 to 20 per cent, will produce a transitory melituria demonstrable by a sensitive and dependable copper reduction test (Benedict's).

Second, the term, "sub tolerance dose," will be used equally to designate that dose, a few grams less than the foregoing, which by like administration fails to produce any demonstrable melituria.

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31 Reiss and Jehn. *Deutsch Arch f klin Med* 108 187, 1912

## SCOPE OF INVESTIGATION AND METHODS EMPLOYED

From the analysis of the earlier work on galactose feeding, it is obvious that nothing was definitely known concerning the real assimilation limit of this sugar. To standardize the present work and establish criteria for later comparisons, the first phase of the study was confined to investigations with so-called normal individuals.

Based on the experience of many years, I feel that a word of caution is not misplaced at this point. In studies of this character, the investigator usually enlists the services of volunteer aids, in many instances students, nurses and colleagues. These individuals, living their normal lives and following their respective vocations, are assumed to be normal, in other words, average. That this assumption is not always warranted any worker in this field will testify. In the present study, several of the subjects, during the course of preliminary standardization, demonstrated evidences of functional or organic derangement. For example two house officers volunteering as subjects, were found to be cases of endocrine hypofunction. In both instances they subsequently stated that they had known themselves to be somewhat at variance from the average, but had attached no importance to it. A still more striking case was observed in another patient, who was studied unknowingly during the development of nephritis. Other cases, as will be brought out in the subsequent discussion, were probably not strictly normal, but as no definite aberration could be detected, they are included in the list. Unsuspected renal glycosurias may be a potent source of error in work of this character unless due precautions are observed and each case subjected to a thorough preliminary testing.

During the earlier part of the work certain highly informative tests now in current use were unavailable. As a preponderance of the subjects here reported did not receive these additional observations, only that part which were common to the entire group will be considered here.

The subjects comprising this group were, in the main, presumably healthy young men and women, either medical students or nurses and interns connected with the hospital. A few other volunteers from outside were also included.

Work of this character is only significant when it is conducted under uniform and carefully controlled conditions, and in which the measurements are quantitative in character. Needless to say, in all analytic procedures the highest obtainable accuracy is the only factor to be considered. To unify external conditions, so far as possible, the subjects all lived at the hospital during the period of study.

To insure approximate nutritional equilibrium, a standard diet was outlined and followed. The subjects received not less than 6 gm. of

carbohydrate, 1.66 gm of protein, and a gross energy intake of not less than 45 calories per kilogram of body weight. Further, as these studies were in no sense exact metabolism investigations, every effort was made to render the diet as varied and palatable as possible. The necessity for exact analysis of the food intake was not operative, and so permitted a most desirable elasticity in the choice of viands. Food values, computed from Locke's<sup>32</sup> compilation, were sufficiently accurate for the purpose. I should like to stress the importance of this aspect in experiments of any duration. The average individual, indifferent alike to the urge of pure science and the enthusiasm of the dietary propagandist, is influenced unfavorably, both directly and indirectly, by the continuance of an unvaried and potentially unpalatable diet.

The standard daily regimen can be presented most succinctly in tabular form.

TABLE 2—Schedule

First day, 7 00 a m	Start collection of first 24 hour urine
7 30 a m	Breakfast Diet begins Physical examination
Second day, 7 00 a m	Complete first 24 hour urine Miscellaneous tests including phenolsulphonephthalein
Third day	Collect second 24-hour urine Nitrogen partition
Fourth day	Repeat second day
Fifth day, 5 00 a m	Empty bladder Ingest 30 or 40 gm galactose in from 10 to 20 per cent solution
7 00 a m	Collect urine G1
9 00 a m	Collect urine G2
9 05 a m	Breakfast
11 00 a m	Collect urine G3
1 00 p m	Collect urine G4
1 05 p m	Dinner
Sixth day	Repeat fifth day, changing dose of galactose by $\pm 10$ gm
Nth day	Collect third 24 hour urine Nitrogen partition II
(N + 1)th day	Repeat second day Diet ends 12 30 p m dinner

The significance of some of the tests given in the foregoing may be touched on briefly. The phenolsulphonephthalein and the careful urine examinations were used as indexes of kidney permeability and the nitrogen partition gave information concerning liver and, by implication, kidney function. All urines were examined for abnormal constituents, while the total nitrogen of the first urine was determined for comparison with those later secured, to ascertain if the prescribed dietary regulation entailed any profound modification of the subjects' usual habitude. As will be seen from the schedule, graded doses of galactose were given until the dose exciting melituria had been determined. In all urines giving a positive response to the qualitative sugar test, the amount of reducing material was estimated quantitatively, and as before stated, the Tollens test applied. Space forbids the discussion of the analytic details of the numerous methods used. It may be said generally that the methods selected were those of proved worth, accuracy being the sole criterion. The galactose test may be permitted a more extended statement.



In all of these experiments only galactose of a demonstrated purity was used. In the earlier tests, the material was obtained from several sources, latterly, the Pfanstiehl product of highest purity has been used exclusively. All were tested thoroughly for purity and doubtful materials were rejected. For the simple assimilation test the technic of administration is as follows. Either at 5 00 a m or 7 00 a m (depending on the other tests to be applied), the patient empties the bladder, the urine being tested for the presence of reducing bodies. The

TABLE 3—Men

Case	Physical		Phenolsulphonephthalein %			Galactose Tolerance		
	Age, Years	Weight, Kg	First Hour	Second Hour	Total	+	0	Lhm
A 1	33	64.3	45	18	63	30	20	<1.00
4	30	65.0	37	24	61	20	10	0.64
16	31	65.8	43	26	69	30	20	2.10
5	30	80.2	29	21	50	30	20	1.15
6	27	68.3	46	19	65	40	30	0.65
7	27	67.0	56	19	75	20	10	0.39
8	39	83.2	—	—	50	40	30	0.39
9	31	69.4	33	21	54	30	20	0.80
10	21	65.8	45	32	77	40	30	1.50
11	20	71.0	49	31	80	30	20	1.20
12	20	69.8	39	32	71	30	20	0.39
13	20	58.5	59	21	79	40	30	0.33
14	23	54.8	53	17	70	30	20	1.43
15	26	56.4	49	23	72	20	15	0.78
18	28	74.3	49	29	78	30	20	0.90
19	24	71.6	45	33	78	30	20	1.13
B 16	70	67.1	19	25	44	40	30	1.74
38	25	58.0	42	35	77	30	20	0.55

## Women

A 1	22	60.4	44	21	65	20	20	1.00
2	31	56.8	35	24	59	40	30	<1.0
3	28	50.0	29	25	54	40	30	<1.0
6	23	58.9	56	16	72	40	30	<1.0
7	24	55.2	40	18	58	50	40	0.22
9	20	52.5	25	22	47	50	40	2.59
10	20	49.2	36	15	51	50	40	2.50
11	19	79.7	37	25	62	50	40	0.35
12	23	47.0	34	29	63	30	20	1.60
14	24	52.7	40	22	62	30	20	1.91
15	26	89.1	38	17	55	40	30	0.25
16	25	54.8	24	28	52	30	20	0.96
18	29	74.3	25	24	49	50	40	2.14
B 14	28	66.3	49	21	70	30	20	0.42
19	52	47.6	61	24	85	40	30	0.60
31	39	62.9	41	34	75	40	30	0.46

test meal of 30 gm of galactose for men and 40 gm for women is administered orally in a cold aqueous solution of from 10 to 20 per cent. The use of lemon or orange juice, as frequently indicated by other observers is carefully avoided. Aside from the fact that it is unnecessary, it introduces a factor of complication in adding varying amounts of foreign sugar. Urine is collected in two two-hour periods, and four hours after the administration of the test meal the subject arises and breakfast is given. The urines are tested qualitatively for the presence of reducing bodies by the Benedict qualitative solution, and where response is positive the amount is determined by the Bene-

dict<sup>3</sup> quantitative titration The slower reduction time of galactose does not introduce a seriously disturbing factor by this method During the earlier tests, a third and fourth two-hour collection of urine was made, but as they were found invariably to be negative, in the later measurements the practice was discontinued

# RESULTS AND INTERPRETATION

Partial results of the study are compiled in Table 3 From the serial numbers designating the subjects, it will be seen that certain cases have been omitted The basis for such omissions were varied, ranging from the nephritis of Case 17A', already alluded to, and the development of a grave condition which ended fatally in Case 2A, to the proven independability of the subject, as was the case with Case 8A' As the thesis was the evaluation of the probable threshold of tolerance, so-called, I felt warranted in discarding those cases where demonstrable

TABLE 4—*Summary of the Collected Data*

	Physical		Galactose Test		
	Age, Years	Weight, Kg	Positive, Gm	Negative, Gm	Excreted, Gm
High					
Male	70	83.2	40	30	2.10
Female	52	89.1	50	40	2.59
Low					
Male	20	54.8	20	10	0.33
Female	19	47.0	30	20	0.25
Average					
Male	29	67.2	31.1	21.3	0.95
Female	27	59.8	40.0	30.0	1.12

pathology negated the normalcy of the case, or where the authenticity of results could be proven lacking The cases from Series B were concerned in another study but were suitable for inclusion here

On the other hand, a few cases were included of which I am suspicious, but as concrete evidence of aberrant function was lacking, they were retained in the group Case 8A falls definitely under suspicion Certain observations unrecorded here are found to be characteristic apparently of certain endocrine conditions It is to be greatly regretted that at the time of this test the basal metabolic rate could not be determined Of the five males showing a positive response at 40 and negative at 30, two, Case 10A and Case 16B eliminate amounts of reducing material, which would show that the probable threshold in the conventional sense is nearer the lower than the higher figure Similarly, of the five women with an upper limit of 50 gm, three fall in the same category

As has already been pointed out, the term, "normal," in such connection implies "average" as its true meaning For this reason summations of the collected data are significant

Such a condensation is given in Table 4

Barring the basic observation that there seems to be a fairly well indicated value for the tolerance of galactose in so-called normal adults, as stated in the foregoing, it is not the purpose of this paper to consider the diagnostic aspects of this work. Bearing on the variations from the calculated average of individuals in the present group, it may be said that endocrine cases have been observed showing much greater deviation from the normal. In male cases the positive dose was severally as high as 80 and as low as 13 gm, while with women a low limit of 5 gm has several times been observed, and in one case, 100 gm of galactose was administered without exciting a melituria. In the light of these facts, the variations here observed lose something of a disturbing significance. The most striking fact here elicited is the evident difference in this level, which must be referred to sex. While I could wish for a larger number of observations on which to base a conclusion, other and later work bears out this conclusion in no unmistakable manner. Pending the completion of investigations now under way, no final conclusion may be drawn, but the fact as observed holds certain attractive possibilities for speculation.

Woman, in her adult years, entertains within her organism a specific galactose mechanism which, so far as is known, is lacking in man. A power of synthesis, of storage and of conjugation of galactose is inherent in the female mammary glands. Grouped among the secondary sex characteristics, coming into development only when sex manifests itself in functional readjustments, it forms a specific point of difference with a specific galactose contact. Whatever the true explanation may be found to be, the fact is certainly interesting and novel.

Certain other aspects may be commented on briefly. In many of the recent studies, the tolerance dosage has been allocated to a relationship with body weight. The Janney<sup>33</sup> technic calls for 1.75 gm of glucose per kilogram of body weight. That this is not warranted in the case of galactose is clearly indicated by the data given here. Relative independence of body weight and tolerance threshold are here manifest. Nor has it been possible to establish other biometric relationship. A comparison of dosage with area calculated by the well known DuBois<sup>34</sup> equation, shows an equal independence. This is repeated in basal metabolism computations (not recorded here), as of course would be expected from the standards involved in such calculations. Age in adults also seems to be without basic influence.

In short, the amount of galactose to be designated under the conventions adopted, as the threshold dose, seems to be a quantity approximat-

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33 Janney, N. W., and Isaacson, U. T. The Blood Sugar in Thyroid and Other Endocrine Diseases, *Arch. Int. Med.* **22** 160 (Aug.) 1918.

34 DuBois, D., and DuBois, E. F. Clinical Calorimetry, *Arch. Int. Med.* **17** 863 (June) 1916.

ing a constant value in healthy adult individuals, and greatly influenced solely by sex among the several biologic factors of potential variation. Later unpublished observations show that with women, the menopause may cause a lowering in the observed level, a fact of supporting significance.

#### SUMMARY

The results of this study may be summarized briefly as follows:

- 1 The significance of the term "threshold of tolerance," for carbohydrates, and the assimilation limit in terms of urine findings is defined.
- 2 Certain necessary control limitations in the application of a provocative melituria test are indicated, and the technic of a test using galactose is described.
- 3 By means of this test, the conventionally defined threshold of tolerance for groups of normal adult men and women is studied and the results reported.
- 4 The dose exciting melituria is influenced little, if at all, by age, weight, body area or certain other biometric factors.
- 5 It is found to be apparently directly dependent on sex, and the influence of the mammary glands in woman is suggested as a possible explanation.
- 6 The average "tolerance dose" for man is found to be 30 gm. and for woman 40 gm.

# THE MUSCULAR EFFICIENCY OF PATIENTS WITH DIABETES MELLITUS<sup>\*</sup>

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The results of a study on the muscular efficiency of a group of patients with diabetes mellitus are presented. Ordinarily, in following cases it is customary for the patient's physician to examine the blood and urine for sugar by quantitative methods, to measure objectively loss or gain in weight and tolerance but to rely on symptoms for a record of loss or gain in physical strength and sense of well-being. Since physical weakness is one of the commonest symptoms of diabetes, and one of its most devastating features from an economic point of view, we thought it important to determine by quantitative methods how weakening a process diabetes may be and to find out what modern methods of treatment can accomplish in the physical reconstruction of sufferers with this illness.

Williams<sup>1</sup> has already studied the problem of muscular efficiency in diabetes by means of the Colin dynamometer. He has shown that diabetic patients tend to be weaker than normal persons and that there is a direct relationship between their food tolerance and muscular vigor. Miles<sup>2</sup> and Root,<sup>3</sup> attacking the question from a somewhat different angle, have shown that the average diabetic patient is not physically fit, using body weight as an index, and furthermore is below normal mentally to various psychologic tests, approaching but not reaching a normal mentality with treatment. On the whole, therefore, it becomes apparent that before the discovery of insulin treatment even the best treated diabetic patient usually carried a handicap in his struggle for existence of a measurably diminished physical and mental efficiency, and too often was compelled to face a slowly progressive course of physical and mental deterioration.

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<sup>\*</sup> From the Medical Clinic of the Peter Bent Brigham Hospital.

<sup>\*</sup> This paper is No. 20 of a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses of this investigation have been defrayed (in part) by a grant from the Proctor Fund of the Harvard Medical School for the study of Chronic Diseases.

1 Williams, J. R. The Effect of Undernutrition on Muscular Force, *Arch Int Med* **20** 399-408 (Sept.) 1917.

2 Miles, W. R., and Root, H. F. Psychologic Tests Applied to Diabetic Patients, *Arch Int Med* **30** 767-777 (Dec.) 1922.

3 Root, H. F., and Miles, W. R. Physical Measurements of Diabetic Patients, *J Metabolic Res* **2** 173-197 (Aug.) 1922.

We have studied the muscular efficiency of a group of twenty-three diabetic patients during the last year, obtaining observations in several cases on the effect of prolonged treatment on strength, using a group of normal persons by way of control. To estimate strength we have used the resistance strength test of Lovett and Martin,<sup>4</sup> a method which we have found simple and accurate. Martin,<sup>5</sup> also, has used the method satisfactorily in studying certain problems of industrial medicine, as has Smith<sup>6</sup> in studies on the strength of soldiers with effort syndrome. For a description of the details and principles of the method we refer to Martin's<sup>7</sup> comprehensive description of it. In brief, the test measures the maximum resistance which various selected muscle groups offer against stretching. From the data so obtained it is possible to calcu-

TABLE 1—*The Strength of Eighteen Normal Men*

Number	Age	Height, cm	Weight, kg	Total Calculated Strength, kg	Strength Weight Ratio
1	30	180	76	2,000	26.6
2	29	171	60	1,600	26.6
3	24	180	78	1,880	23.6
4	29	173	57	1,320	23.0
5	27	166	57	1,290	22.6
6	23	172	62	1,350	21.7
7	24	180	64	1,370	21.6
8	42	170	48	1,030	21.6
9	25	177	76	1,630	21.4
10	30	175	70	1,480	21.0
11	22	169	61	1,270	20.7
12	30	174	63	1,300	20.5
13	21	189	89	1,810	20.3
14	23	185	64	1,270	19.9
15	29	182	74	1,450	19.6
16	23	176	84	1,540	18.4
17	26	180	65	1,120	17.3
18	37	181	78	1,230	15.7
Average				1,440	21.2

late the entire muscular strength of the body. The result is expressed in kilograms of total strength or perhaps more accurately in the ratio between strength and weight. We have used for muscle examples those muscle groups advocated by Martin in the abbreviated strength test and used by Smith in his study, namely the right and left pectorals, the right and left wrist flexors, the right and left forearm flexors, the right and left thigh adductors and the right and left thigh abductors.

4 Lovett, R. W., and Martin, E. G. The Spring Balance Muscle Test, *Am J Orthop Surg* **14** 415-424 (July) 1916.

5 Martin, E. G. Strength Tests in Industry, *Pub Health Rep* **35** 1895-1926 (Aug 13) 1920.

6 Smith, B. The Possibilities of Physical Development in Cases of Effort Syndrome by Means of Graded Exercises, *Arch Int Med* **24** 321-331 (Sept) 1919.

7 Martin, E. G. Tests for Muscular Efficiency, *Physiological Rev* **1** 454-474 (July) 1921.

Table 1 records our observations on single strength tests in a group of normal men. We found that the total strength, as estimated by a single determination with the method in our hands, varied between 1,100 and 2,000 kg with an average of 1,441. The strength-weight ratio varied between 26.6 and 15.7 with an average of 21.2. Martin and Rich,<sup>8</sup> studying the strength of a large number of normal men with this method, found total strength figures varying from 910 kg to 2,640 kg with an average of 1,800 kg and strength-weight ratios ranging from 19 to 37 with an average of 26.6. Our normal men, therefore, were weaker on the whole than the larger series of Martin and Rich. Our subjects were house officers and medical students, while Martin and Rich's were perhaps in better training as they included college

TABLE 2—*The Strength of Eighteen Normal Women*

	Number	Age	Height, Cm	Weight, Kg	Total Calculated Strength, Kg	Strength Weight Ratio
1		26	148	39	730	18.7
2		24	166	54	940	17.4
3		23	159	61	1,060	17.3
4		22	175	57	970	16.6
5		21	163	51	810	16.0
6		20	169	70	1,120	16.0
7		21	170	62	950	15.4
8		21	160	52	810	15.4
9		22	167	53	790	14.9
10		20	162	48	720	14.9
11		21	166	52	760	14.6
12		19	160	54	760	14.1
13		20	159	54	750	13.9
14		28	167	70	930	13.3
15		23	159	53	700	13.1
16		21	166	62	795	12.8
17		30	164	59	750	12.7
18		23	168	67	780	11.7
Average					840	14.9

students and recent army recruits. Furthermore, their figures are the average of more than one determination. However, our men were strong enough to work hard, therefore we have used our figures as a normal base line and have compared the strength of our male diabetic patients with our average normal male strength figure and strength-weight ratio.

Table 2 records similar observations on single strength tests in a group of normal women. We found that the total strength varied between 700 and 1,100 kg, with an average of 839. The strength-weight ratio varied between 11.7 and 18.7 with an average of 14.9. Here again our subjects were weaker than Martin's 116 factory workers, who had an average strength of 900 kg and strength-weight ratio of

8 Martin, E. G., and Rich, W. H. Muscular Strength and Muscular Symmetry in Human Beings, *Am J Physiol* 47:29-42 (Sept) 1918.

163, and considerably weaker than Mosher and Martin's<sup>9</sup> forty-five college women, with an average strength-weight ratio of 22.5

Our women were pupil nurses, secretaries, or technicians who volunteered to act as controls. Some were on night duty at the time the test was made, so that loss of sleep may have been a factor in causing our low figures. However, all were strong enough to carry on their routine work, therefore we have used our figures as a normal base line, and have compared the strength of our female diabetic patients with our average normal female strength figure and strength-weight ratio.

Since one of the main objects of our study was to make repeated strength tests on patients for a reasonable period of time, it was necessary to determine the variations in strength occurring in normal persons from day to day as detected by the method. For this purpose we made daily strength tests for a month on each of five normal men, and weekly strength tests for a period of six weeks on each of seven other normal

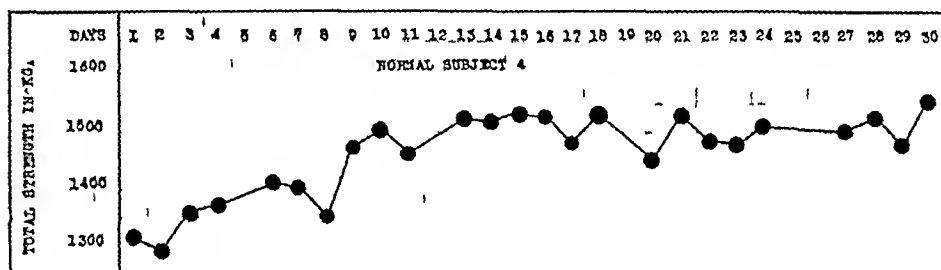


Chart 1—The daily variation in strength of a normal man

men. In the daily strength tests we found a tendency for total strength to increase for the first few determinations, and thereafter to remain at a fairly constant level. In the weekly strength tests we found a slight variability, but no tendency for the graph to deviate to any great extent from a straight line. We found, however, appreciable temporary variations in strength caused by loss of sleep, minor infections, and exercise before the test was made. Typical examples of these points are tabulated.

Chart 1 records the strength curve of a normal subject, and is composed of twenty-five determinations made during the course of a month's observation. During the first nine days there was a progressive rise in strength until a constant level was gained. Subsequently the strength varied but little until the experiment was ended. The initial rise in strength was in all probability due to practice, while the subsequent straightness of the line illustrates the limits of constancy which are obtainable by the method when the test is used on a trained subject. All determinations were within 12 per cent of the mean, showing that the technical errors of the method are not too great for clinical purposes.

<sup>9</sup> Mosher, C. D., and Martin, E. G. The Muscular Strength of College Women, *J. A. M. A.* 70: 140-142 (Jan. 19) 1918.



Chart 2 records details from the strength curves of two normal subjects to illustrate the effect of infection, exercise, and loss of sleep on strength. Each of these factors caused an appreciable though temporary loss in strength. The chart is plotted to magnify the variations in strength which were observed.

From such evidence, therefore, we believe that Lovett and Martin's method of testing strength is sufficiently accurate for clinical purposes. By using it, we were able to establish a normal base-line of strength with which to compare the strength of patients with diabetes, and we were able to show that strength in a normal individual remains relatively constant when followed for any length of time although it is modified temporarily by such factors as loss of sleep, infection or exercise. We

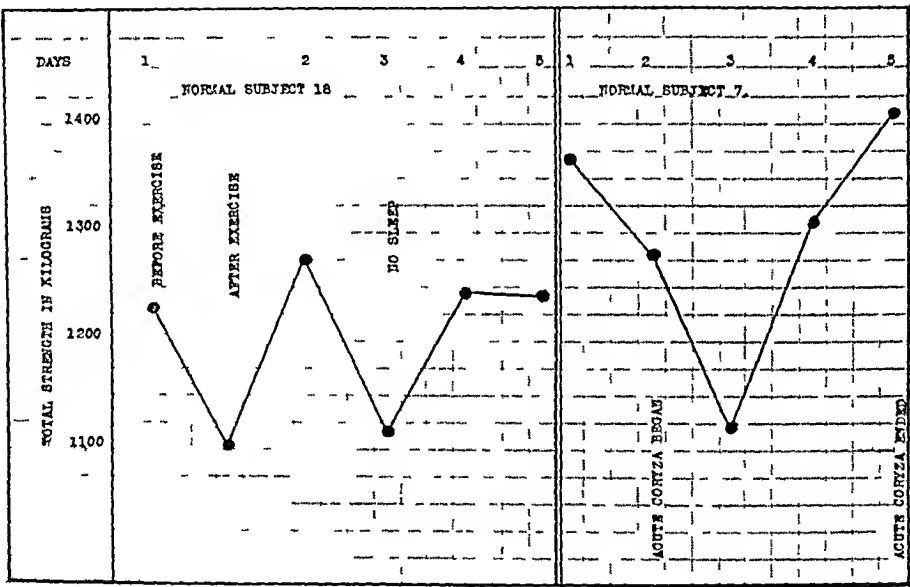


Chart 2—The effect of exercise, loss of sleep, and an acute infection on strength

have used as an average figure of normal strength our figures of 1,440 kg for men and 840 kg for women, we have considered the normal strength-weight ratio of men 21.2 and of women 14.9.

Table 3 records single strength tests on a group of fourteen adult male diabetic patients. These strength tests were made, with one exception, shortly after the patients entered the hospital and before treatment had been followed for any length of time. Case 5 was one of Joslin's<sup>10</sup> patients, who has faithfully carried out treatment under his guidance for ten years. While the diabetic group as a whole was older and less heavy than the normal group, a comparison between the two

<sup>10</sup> Joslin, E. P. The Treatment of Diabetes Mellitus, Philadelphia, Lea and Febiger, Ed. 3.

brings out two important features. The average strength of the diabetic group was considerably less than normal, ranging from 760 to 1,430 kg in contrast to the normal range of between 1,100 and 2,000 kg. Moreover, the diabetic patients were not only weak from loss of body tissue but tended to be weaker than normal in proportion to their weights, because the average diabetic strength-weight ratio was 18.8 with a range

TABLE 3—*The Strength of Fourteen Diabetic Men*

Number	Age	Height, Cm	Weight, Kg	Total Calculated Strength, Kg	Strength Weight Ratio	Duration of Diabetic Symptoms
1	30	165	47	1,210	25.8	3 years
2	16	170	45	1,140	25.0	2 years
3	42	175	63	1,430	22.7	4 years
4	26	178	53	1,200	22.5	8 months
5	40	177	50	1,020	20.4	10 years
6	43	168	56	1,010	18.0	4 years
7	37	177	71	1,270	17.9	1 month
8	48	183	65	1,160	17.8	2 years
9	38	172	49	850	17.5	9 months
10	28	170	49	850	17.3	5 months
11	22	174	60	1,020	16.9	2 years
12	36	169	53	760	14.2	3 years
13	53	176	56	775	13.9	7 years
14	52	177	50	690	13.9	5 years
Average				1,000	18.8	

of from 13.9 to 25.8, in contrast to the normal average of 21.2 with a range between 15.7 and 26.6.

Five of these patients (Cases 9, 10, 12, 13 and 14) when we first saw them had less than 60 per cent of a normal man's strength. This gives an idea of how weakening a process diabetes may become. Of these five patients, two died within a few months from the time we first saw them, two have improved remarkably and we have lost track

TABLE 4—*The Strength of Five Diabetic Women*

Number	Age	Height, Cm	Weight, Kg	Total Calculated Strength, Kg	Strength- Weight Ratio	Duration of Diabetic Symptoms
1	41	165	47	840	18.0	4 months
2	21	156	38	625	16.5	18 months
3	18	160	42	620	14.6	4 months
4	33	160	40	540	13.5	8 months
5	23	165	52	600	11.5	3 months
Average				645	14.8	

of the other one. The rapidity with which the two fatal cases succumbed despite the use of insulin, suggests that extreme physical weakness may be of prognostic significance.

The duration of symptoms appeared to have little to do with the amount of weakness measured. Rather, one gets the impression that the most neglected patients grew weak most rapidly and that the ones that made any attempt to take care of themselves conserved strength the longest.

Table 4 records single strength tests on the five diabetic women of the series. The findings in this group are similar to those obtained in the men. The average age of the patients was greater and the weight less than that of the normal group. The average diabetic strength was considerably less than normal, ranging from 540 to 840 kg, in contrast to the normal range of between 730 and 1,120 kg. One interesting difference between the diabetic men and women, however, was the apparent normality of the diabetic women's strength-weight ratio. The average strength-weight ratio of the diabetic women was 14.8 against the normal variation of 14.9. The variations encountered ranged between 11.5 and 18.0, while the normals variation ranged between 11.7 and 18.7. This finding may be accidental, as the series was very small.

Systematic exercise is usually considered to be a part of the treatment of diabetes. On this account we attempted to find out whether the diabetic patients' physical weakness was evenly distributed, or whether it was due to an exaggerated weakness of any specific muscle.

TABLE 5—*Composite Strength Test of Normal Men*

Age 27, Height 176 Cm, Weight 68 kg, Total Calculated Strength 1,430 kg, Strength Weight Ratio 21.0

Muscles		Strength, Kg	Per Cent Total Strength
Pectoral	Left	34	2.4
	Right	36	2.5
Wrist flexor	Left	22	1.5
	Right	22	1.5
Forearm flexor	Left	32	2.2
	Right	31	2.2
Thigh abductor	Left	19	1.3
	Right	20	1.4
Thigh adductor	Left	18	1.3
	Right	19	1.3

group which might be overcome by appropriate physical therapy. Martin has shown that the sum of the strengths of the individual muscles tested constitutes in men 17.7 per cent, and in women 18 per cent, of the entire strength as found by this system of testing. By making a composite strength test from the individual subjects of the series, and analyzing the relative distribution of strength, we were able to obtain data on the distribution of the strength of normal and diabetic persons.

Table 5 records a composite strength test made from the eighteen normal men of Table 1. The resulting man was aged 27, 176 cm (5 feet, 9½ inches) tall and weighed 68.2 kg (150 pounds) in his clothes. His total strength was 1,430 kg and his strength-weight ratio was 21. Of his strength, 4.9 per cent came from his pectoral muscles, 3 per cent from his wrist flexors, 4.4 per cent from his forearm flexors, 2.7 per cent from his thigh abductors and 2.6 per cent from his thigh adductors.

Table 6 records a similar composite strength test made from the fourteen diabetic men of Table 3. The resulting man was aged 37, 174 cm (5 feet, 8 $\frac{3}{4}$  inches) tall and weighed 54.8 kg (121 pounds) in his clothes. His total strength was 1,020 kg and his strength-weight ratio was 18.6. Of his strength, 4.6 per cent came from his pectoral muscles, 3.3 per cent from his wrist flexors, 4.7 per cent from his forearm flexors, 2.7 per cent from his thigh abductors and 2.5 per cent from his thigh adductors.

TABLE 6—*Composite Strength Test of Diabetic Men*

Age 37, Height 174 Cm, Weight 55 Kg, Total Calculated Strength 1,010 Kg, Strength-Weight Ratio 18.4

Muscles		Strength, Kg	Per Cent Total Strength
Pectoral	Left	22	2.2
	Right	24	2.4
Wrist flexor	Left	16	1.6
	Right	17	1.7
Forearm flexor	Left	23	2.3
	Right	24	2.4
Thigh abductor	Left	12	1.2
	Right	15	1.5
Thigh adductor	Left	12	1.2
	Right	13	1.3

In other words our normal man, according to medical-actuarial statistics was about 8 pounds (3 kg) under standard weight for one of his years and size, while our diabetic man was about 40 pounds (18 kg) under standard weight. Besides being undernourished, the diabetic man was weaker than normal because he was only about 70 per cent as strong as the younger normal man, and this weakness did not depend on

TABLE 7—*Composite Strength Test of Normal Women*

Age 21, Height 164 Cm, Weight 57 Kg, Total Calculated Strength 840 Kg, Strength-Weight Ratio 14.7

Muscles		Strength, Kg	Per Cent Total Strength
Pectoral	Left	18	2.1
	Right	19	2.3
Wrist flexor	Left	13	1.5
	Right	13	1.5
Forearm flexor	Left	18	2.1
	Right	19	2.3
Thigh abductor	Left	14	1.7
	Right	14	1.7
Thigh adductor	Left	12	1.4
	Right	12	1.4

undernourishment solely because his strength-weight ratio was diminished. He was not weak, however, in any specific muscle group, because the contributions of the muscle groups studied to the total strength were essentially the same as in the normal.

Table 7 records a composite picture of our group of normal women. The resultant subject was aged 21, 164 cm (5 feet, 4 $\frac{3}{4}$  inches) tall

and weighed in her clothes 56.6 kg (124 pounds). Her total strength was 845 kg and her strength-weight ratio was 14.9. Of her strength 43 per cent came from her pectoral muscles, 31 per cent from her wrist flexors, 43 per cent from her forearm flexors, 34 per cent from her thigh abductors and 28 per cent from her thigh adductors.

Table 8 records a composite strength test from the diabetic women. The resultant subject was 27 years old, 161 cm (5 feet 3½ inches) tall and weighed in her clothes 43.8 kg (91 pounds). Her total strength was 645 kg and her strength-weight ratio was 14.7. Of her strength, 44 per cent came from her pectoral muscles, 34 per cent from her wrist flexors, 46 per cent from her forearm flexors, 30 per cent from her thigh abductors, and 27 per cent from her thigh adductors.

TABLE 8—*Composite Strength Test of Diabetic Women*

Age 27, Height 161 Cm, Weight 44 kg, Total Calculated Strength 650 Kg, Strength Weight Ratio 14.8

Muscles		Strength, Kg	Per Cent Total Strength
Pectoral	Left	14	2.2
	Right	14	2.2
Wrist flexor	Left	11	1.7
	Right	11	1.7
Forearm flexor	Left	15	2.3
	Right	15	2.3
Thigh abductor	Left	10	1.5
	Right	10	1.5
Thigh adductor	Left	9	1.4
	Right	8	1.2

Our normal woman was 4 pounds (1.8 kg) under standard weight for one of her age and size. Our diabetic woman was 35 pounds (15.9 kg) under standard weight for one of her age and size. Our diabetic woman, therefore, was undernourished and weak although she was not weak out of proportion to her weight, having a normal strength-weight ratio. There was no specific muscle group weakness, because the contribution of the muscle groups studied to total strength was essentially similar in both groups.

From these data it is suggested that the best form of physical therapy for a diabetic patient is any general form of exercise directed toward improving the entire physique. Since the diabetic patients' weakness is not due to the weakness of any specific group of muscles, massage, mechanotherapy or exercise directed to any single muscle or small group of muscles is not indicated.

There may be secondary factors causing the weakness of a diabetic person other than the primary factor of prolonged undernutrition and underweight. This is suggested by a comparison of the strength test of Case 8 of the normal men with Case 5 of the diabetic men. The data are recorded in Table 9.

The normal subject was 50 pounds (22.7 kg) under standard weight for one of his years and size, while the diabetic subject was 58 pounds (26 kg) under standard weight. Both had the same amount of total strength and essentially normal strength-weight ratios. The normal man was stronger in the pectoral and forearm muscles than the diabetic subject, while the diabetic man compensated for this weakness by being stronger than the normal man in his leg muscles. The normal man had been thin all his life and was able to lead a very normal and productive life as a physiologist. The diabetic patient had been under treatment for ten years, unable to do a full day's work and gradually losing weight but keeping up strength by systematic exercise. The two men were in a way comparable as physical specimens at the time of the strength test, for it is needless to say that both were normal to physical

TABLE 9—*Comparison in Strength Between a Normal and Diabetic Subject*

		1 Normal Age 42, Height 170 Cm (5 Ft 7 In ), Weight 48 Kg (106 Lbs ), Strength in Kg	2 Diabetic Age 40, Height 177 Cm (5 Ft 10 In ), Weight 50 Kg (110 Lbs ) Strength in Kg
Pectoral	Left	26	19
	Right	27	23
Wrist flexor	Left	16	16
	Right	16	16
Forearm flexor	Left	23	20
	Right	26	23
Thigh abductor	Left	12	15
	Right	14	16
Thigh adductor	Left	11	16
	Right	11	16
Total strength		1,030	1,020
Strength weight ratio		21.6	20.4

examination and both had normal urines. As one saw the two men, the striking difference between them was in their mental attitude. The normal man was eager, quick in his motions and working mentally at top speed. The diabetic man, in contrast, was not eager, was slow in all his motions and was working mentally at a slow speed. The basal metabolic rate of the normal man was known to be normal, Joslin informs us that the metabolic rate of the diabetic patient was minus 18 at about the time the strength test was made. Therefore, the chief objective difference between the two men lay in the difference of their basal metabolism. One cannot but wonder from such a comparison how much the factor of suboxidation has to do with producing the clinical picture of chronic diabetes where a low metabolism is found so frequently.

On the whole, these preliminary observations on the strength of diabetic patients brought out the following points: the majority of the men and women of the series tended to be considerably weaker than normal persons but without any specific weakness of any of the muscle

groups studied. The diabetic men were not only weak because they tended to be underweight, but were weaker than normal in proportion to their diminished weights. The women, on the other hand, appeared to be weak solely because they were undernourished and tended to be normally effective in proportion to their body weights. A comparison between a normal thin man and a chronic well treated diabetic patient of approximately equal size and age showed that the two subjects had the same amount of strength, the normal subject, with normal basal metabolic rate, was much more alert and keen than the diabetic subject who with a metabolic rate, was sluggish mentally and physically. This observation suggested that other factors than chronic inanition may play a part in producing the clinical picture of long-standing diabetes.

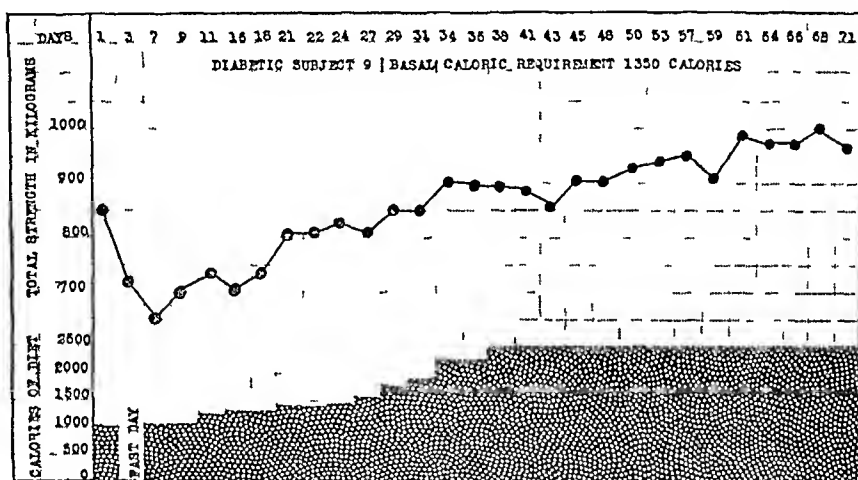


Chart 3—The relation between the calories of the diet and strength in a diabetic patient

We<sup>11</sup> have already shown by illustrative strength curves that certain patients with severe diabetes may gain a great deal of measurable strength during treatment. It is of interest to analyze how strength is gained. The most important single factor which gives a diabetic patient strength appears to be the total calories of the glycosuria free diet utilized. This point is illustrated by Chart 3.

The patient was a man, aged 38, with diabetes of about nine months' duration. When he entered the hospital he had lost about 50 pounds (22 kg) in weight and was very weak.

During the interval in which he received less calories than his basal requirement, he failed to gain strength and even lost slightly. It was not until he was given calories well above his basal requirements that he gained perceptibly, and it appeared to take several days for him to

<sup>11</sup> Fitz, Reginald, and Murphy, W. P. Insulin as an Investment for the Patient with Diabetes Mellitus, J. A. M. A. 82:435-438 (Feb. 9) 1924.

recover the strength which was lost during the period of greatest under-nutrition. We have made confirmatory observations on the weakening effect of undernutrition in several other cases, on this account we now desugarize the patients with severe diabetes with insulin as soon as they come into the hospital, and no longer use very low calory diets for more than a day or two, as the strength lost by such treatment seems out of proportion to the tolerance gained.

Unfortunately we have not succeeded in making any critical observations on the strength yielding properties of diets variously balanced in respect to their carbohydrate, protein and fat fractions. Such evidence as we have, however, suggests that weak diabetic patients will gain strength satisfactorily when given diets containing about 1 gm of

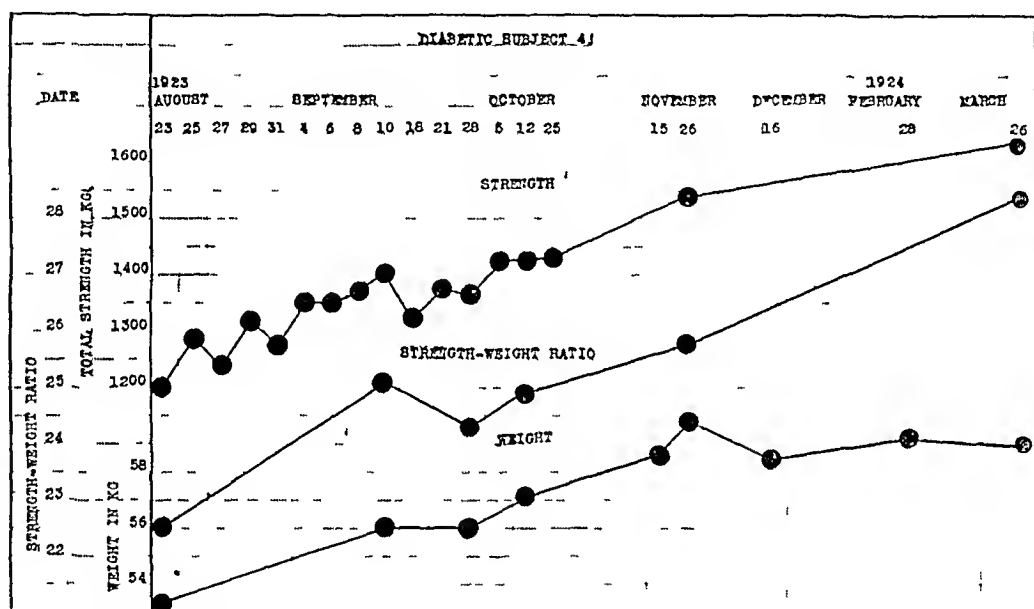


Chart 4—The relation between strength and weight in a well treated diabetic patient

protein and about 45 calories per kilogram of body weight. It seems to make but little difference in what form the calories are given so long as the fat proportion is not enough in excess to cause acidosis, and so long as the urine remains sugar-free.

From the point of view of strength, it appears that the best treatment for a diabetic patient should combine an adequate diet with adequate physical exercise, so that as the patient gains weight he gains a more than proportional amount of strength and thus has an increasing strength-weight ratio. One of the temptations offered by insulin is the possibility of fattening diabetic patients rapidly. We have three patients who became fat under insulin treatment gaining weight more rapidly than they gained strength, and these patients do not seem as well or as physically efficient now as those that have gained strength



more rapidly than they have gained weight. On this account we do not believe in using very high calory diets and large amounts of insulin, in order to obtain an immediately striking therapeutic result, but prefer to have our patients take less to eat, use smaller amounts of insulin and to gain weight and strength slowly. The strength curve of a patient under observation for seven months and treated conservatively in this fashion is recorded in Chart 4.

The patient was a man, aged 20, 178 cm (5 feet 10½ inches) tall, weighing 53.4 kg (117 pounds) in August, when we first saw him. His basal caloric requirements at that time were 1,600 calories, and at the beginning of treatment the patient was about 40 pounds (18 kg) under standard weight. Fortunately his strength had not been much depleted during the eight months he had diabetes, so that his physical condition was fairly good. Since he came to the Brigham Hospital he has taken each day a diet containing about 2,500 calories and 60 gm of protein. On this diet he has gradually gained 6 kg (13 pounds) in weight. With this gain in weight, which still leaves him more than twenty-five pounds under standard weight, he has increased his strength markedly and now has a very high strength-weight ratio. It so happens that he is an insurance broker forced to do considerable walking each day in his business, and thus he has been compelled by economic reasons to take an adequate amount of exercise. He has gained but little weight during the last three months, although his strength and strength-weight ratios have increased steadily. When we last saw him he felt in perfect health, was able to work as hard as he chose without undue fatigue and he was stronger than our average normal man. We have advised this patient to keep his weight at about its present level and have warned him against gaining more than a few extra pounds.

#### SUMMARY

On the whole, from these studies on the muscular efficiency of patients with diabetes we have obtained evidence confirming the observations of Williams and of Miles and Root. The strength of most diabetic patients is appreciably less than normal, but can be made to approach normal by proper diet and physical therapy. The total calories of the diet rather than the fractions of carbohydrate, protein or fat, seem of greatest importance in adding strength.

Since there is no selective weakness of any particular muscle group which characterizes diabetes, any general form of exercise which will bring all the muscles into play is indicated from the point of view of physical therapy.

Undernutrition for any length of time is weakening and should not be recommended for more than a day or two as the strength lost

by such treatment is out of proportion to the tolerance gained. The best treatment for a diabetic patient should combine diet and physical exercise, so that as the patient gains weight he gains a more than proportional amount of strength and an increasing strength-weight ratio. Diabetic patients should not be fattened rapidly with insulin and high calory diets. Such patients do not become as physically efficient as patients who gain weight more gradually on a lower diet and less insulin, and who remain thin but relatively strong with high strength-weight ratios.

# Book Review

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GENERAL AND EXPERIMENTAL PATHOLOGY By HERMANN PFEIFFER,  
Professor at the University of Graz Pp 594, 50 illustrations, 8 color  
plates Berlin and Vienna, Urban and Schwarzenberg, 1924

An ever widening foundation of biochemistry, biophysics and physiology form the basis of our understanding of pathologic processes and clinical manifestations of disease To present an even superficial view of this vast fabric of interrelated basic phenomena in a single volume seems an almost hopeless task, the more so when it is to be made useful for students of medicine rather than the more mature Krehl succeeded in a singularly striking fashion, due, no doubt, to his marvelous grasp of the material We now possess three additional efforts in the same direction, those of Herring, of Ludke and Schlayer, and of Pfeiffer, here reviewed In its subject matter Professor Pfeiffer's work is also a pathologic physiology

There can be no doubt as to the importance of the subject or of the value of the systematic and orderly treatment of the material for the student Teachers of medicine realize only too well that much of the most valuable and important "borderline" knowledge that the student should possess is never presented to him in any organized series of lectures, certainly never from the medical point of view This whole group of German texts seems of particular value in bridging this gap, it is unfortunate that they may seem so formidable that the medical student would hardly find the time to use them

Pfeiffer's book covers the extrinsic causes of disease, inflammation and fever, immunity, the blood diseases and circulation, respiratory alterations, metabolism, the glands of internal secretion and experimental tumors The general character of the work is exemplified in a chapter of 110 pages on internal secretion, in which a most objective summary is presented, the chapter on "Inflammation" and on "Fever" are particularly readable

The investigator will perhaps miss references, purposely omitted to permit condensation, but will be rewarded by an excellent review of the best work in the fields covered It is to be regretted that we have no English counterpart of this and the similar books, they would be of great value to the serious medical student in his transition from the laboratory to the clinic, a transition which in the majority of our medical schools is harmful because of its abruptness

To the fact that the text has been written by a single person must be credited the absence of reduplication and redundancy in the book, and the fact that the proper proportion has been maintained in the various sections

## SURGICAL TREATMENT OF ANGINA PECTORIS

REPORT OF EIGHT ADDITIONAL CASES AND REVIEW OF LITERATURE

PHILIP KING BROWN, M D

AND

WALTER B COFFEY, M D

SAN FRANCISCO

When we undertook to relieve angina by following the suggestion of Franck as carried out first by Jonnesco,<sup>1</sup> we were fully conscious that all that had been accomplished by Jonnesco's first operation was to relieve the substernal anginal pain and the associated referred pains in his patient, by a removal of the left cervical sympathetic system and the upper thoracic ganglion. The functions of much of the removed parts were the subject of some important differences of opinion, and certainly many tracts transmitting a variety of impulses were severed in Jonnesco's operation. It seemed to us wise, therefore, to simplify if possible this complex situation by beginning at one end of the tract and severing as few connections as possible, continuing to interrupt paths between heart and brain and cord until we found just what brought the relief.

Our first four patients<sup>2</sup> were operated on by severing merely the main left sympathetic trunk below the superior ganglion, and the superior cardiac branch. In the fifth patient the ganglion was removed, because the superior cardiac trunk arose in part from that by at least one and we thought possibly by several roots. Besides this, the fourth patient had had pain recur in the left forearm, although the substernal pain had been relieved. That other branches through vagus connections might be of influence in relaying sensation seemed possible, and the consequences of a removal of the ganglion seemed insignificant as compared to the incomplete relief of pain. Since that time, the superior

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1 Jonnesco, T. Angine de poitrine, guerie par la resection du sympathique cervico-thoracique, Bull de l'Acad de med, Paris **84** 93 (Oct 5) 1920, Le traitement chirurgical de l'angine de poitrine, ibid **86** 67 (July 19) 1921, Traitement chirurgical de l'angine de poitrine par la resection du sympathique cervico-thoracique, Presse med **20** 193 (March 9) 1921, La resection du sympathique cervico-thoracique, technique operateure, Presse med **30** 353 (April 26) 1922

2 Coffey, W B, and Brown, P K. The Surgical Treatment of Angina Pectoris, Arch Int Med **31** 200-220 (Feb ) 1923

ganglion has always been removed. One patient (Case 3) of the first group has been operated on a second time, after the failure of section of the main trunk and superior cardiac branch to relieve permanently the pain referred to the region of the heart apex and left arm, and the occurrence of new pain in the back behind the heart in the vicinity of the angle of the left scapula. That case is not counted in the new group, although it will be discussed as Case 9 in the light of the further relief of the patient's pain after the second operation, in which the superior ganglion was removed after merely the severance of its main trunk and the superior cardiac connections in the first operation. Case 8<sup>3</sup> was reported in full and it contributes one more fact to the slowly accumulating data regarding angina, and heart and aorta innervation. In that case the pains were substernal but the radiations were dextral and a right-sided operation, in which the superior ganglion was removed, caused complete relief from attacks.

Of this group of additional cases, one (Case 1) patient died a cardiac death within a few hours of the operation and another patient (Case 5) in two weeks, also of heart failure. Both had low blood pressure, large flabby hearts and negative T waves in Lead I. The pains in both were substernal, but also in the apex region as well as down the left arm. In Case 1 the death of the patient was unexpected and hard to explain. In Case 5 the death of the patient was not unexpected. He had consumed alcohol and opiates to excess for years, was extremely obese, and had a chronic cough and an extreme dyspnea at the time of operation. The attacks were so numerous and severe that he was in pain day and night, and the operation was recognized as a desperate chance.

The other operations were brilliant successes, so far as relief of the agonizing substernal pain of angina goes. The patients were all restored to comfort and some degree of usefulness, depending on the underlying heart condition. One patient still has severe pain for a second or two in the angle of the left jaw when he begins to chew food, and he and one other have had pain in the posterior part of the left apical region above the center of the scapula. There is not only pain on pressure but pain when the shoulder is raised from extension of the left arm at right angles to the body. These pains in jaw and left shoulder have occurred, to some degree, after six of the fourteen operations done (on thirteen patients) and have been of minor consequence, disappearing in a few weeks in all but two patients. The jaw pain seems to be due to pressure from retraction on the anterior auricular nerve, and the left posterior shoulder region pain must be due to injury of some connection of the nerve and ganglion.

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3 Brown, P. K. Cervical Sympathectomy for Angina Pectoris. Report of a Case with Dextral Radiations of Pain, *J. A. M. A.* 80: 1692-1693 (June 9) 1923.

Two patients (Cases 6 and 9) have had pain in the region of the heart apex, and in the region of the angle of the left scapula and down the left arm

Whether we have gone too far in removing the superior ganglion was and is still a matter of some doubt. Important light on the subject is to be looked for in one patient, in whom pain returned after one and one-half years, and whose pain was apparently relieved by removal of the superior ganglion which was not removed at the first operation (details given in Case 9). If the patient continues free from pain under present conditions, there must be connections between heart and spinal cord that were interrupted by this procedure. Should the pain return again in the region of the heart apex and in the arm, it is still possible to do one of two things, remove the two lower ganglions in the sympathetic chain and the upper thoracic or cut the sensory roots in the spinal canal.

It must not be forgotten that complete relief of the main and severest pain, and to our minds the most serious symptom of angina, came from the operation of cutting only the main sympathetic trunk and the superior cardiac nerve on the left side. In the light of this, one fact stands out clearly, that the substernal pain is a spasm of the first part of the aorta where the superior cardiac branch is largely distributed, and it is the vasoconstrictor influence of this nerve, not only to the aorta but the coronaries which it also supplies, that is responsible for the main symptom of angina. Death occurs when this constrictor action on both aorta and coronaries deprive the heart of blood, and this effect is contributed to by sclerosis of both the aorta and the coronary vessels. It is possible that constrictor impulses are relayed to some extent by the middle ganglion, which, according to some authors (Figs 1 and 2) may give off a branch to the superior cardiac nerve below where it was cut in our operation. This would account for the persistence of certain referred pains in a few of the cases.

There is one other point that needs consideration, and on which light can only come from developments in patients already operated on, and that pertains to the work of Wenckebach,<sup>4</sup> and Eppinger and Hofer in Vienna. Wenckebach reported five cases in which the depressor nerve was resected on the left side. This nerve, according to Krielman, arises by two roots, one from the superior laryngeal and the other from the vagus. These two join, forming a cord which soon unites with the vagus. Finkelstein<sup>5</sup> found this branch in only two of five cadavers. Békésy found it in nine out of fourteen cadavers, and states that it runs isolated for only 1 cm and then joins the vagus again. It exists as a

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4 Wenckebach, K. F. Deutsch-Internisten Kongress, Vienna, April, 1923

5 Finkelstein. Der Nervus depressor beim Menschen, Kaninchen, Hunde, bei der Katze und dem Pferd, Arch. f. Anat. u. Phys. Anat. Abt., 1880, p. 245

separate nerve in animals according to von Cyon<sup>6</sup> The existence of a separate depressor nerve in man is denied by American physiologists and anatomists, so far as we have been able to carry our search Odermatt<sup>7</sup> reviews the literature on this nerve, and describes an attempt to cut it in a case of bad angina Hotz of Basel operated under local anesthesia on a man, aged 65 years, who had had scarlet fever and rheumatism in youth A diagnosis of tetany and syphilis was made

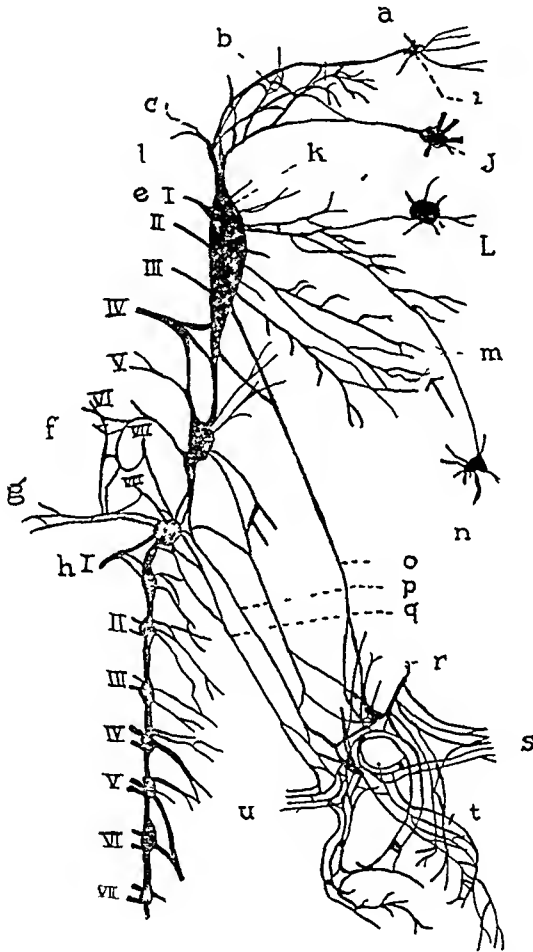


Fig 1—The cervical and dorsal sympathetic systems, with connections to spinal cord and vagus *a*, cavernous plexus, *b*, internal carotid plexus, *c*, rami communicantes between gangliated cord and *d*, ganglion jugulare, *e*, cervical nerves I, II, III, IV, V and VI, *f*, plexus about vertebral artery VII, *g*, plexus about subclavian artery VIII, *h*, thoracic nerves I, II, III, IV, V, VI and VII, *i*, ciliary ganglion, *j*, sphenopalatine ganglion, *k*, ganglion nodosum vagus, *l*, otic ganglion, *m*, connections with vagus and glossopharynx to form pharyngeal plexus (inhibitory), *n*, submaxillary ganglion, *o*, *p* and *q*, superior, middle and inferior cardiac nerves (accelerator), *r*, connections with vagus and recurrent laryngeal nerves (inhibitory), *s*, left pulmonary plexus, *t*, cardiac plexus, *u*, right pulmonary plexus

<sup>6</sup> Von Cyon Die Nerven des Herzens, Übersetzt v Heusner, Berlin, J Springer, 1907

<sup>7</sup> Odermatt, W Deutsch Ztschr f Chir **182** 341 (Sept) 1923

in 1921 For four years he had had cramps in the hands and stasis in the veins The Wassermann test was positive Blood pressure at this time was 170 An antisiphilitic treatment left him free from trouble for one and one-half years Following this, he began to have pressure in the heart region, air hunger, anxiety, and pain in the right shoulder In the hospital he continued to have attacks more and more frequently, in spite of much rest in bed and general treatment The pains radiated to the left shoulder blade and arm, as many as four attacks occurring in one day

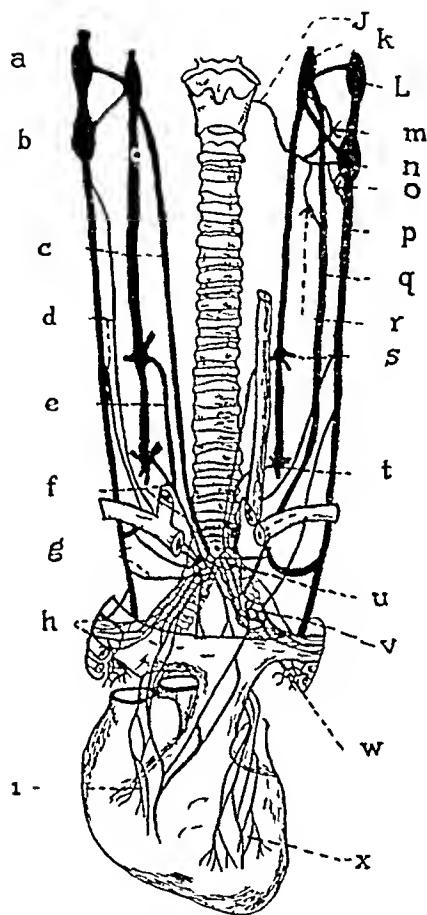


Fig 2—Cardiac, pulmonary and coronary plexuses, *a*, ganglion of root (inhibitory), *b*, ganglion of trunk (inhibitory), *c*, superior cardiac nerve (accelerator), *d*, cervical cardiac branches of vagus (inhibitory), *e*, middle cardiac nerve (accelerator), *f*, inferior cardiac nerve (accelerator), *g*, thoracic-cardiac branches of vagus (inhibitory), *h*, right inferior pulmonary plexus, *i*, right coronary plexus, *j*, superior laryngeal, *k*, superior cervical ganglion (accelerator), *l*, ganglion of root (inhibitory), *m*, branch from superior cervical ganglion, *n*, ganglion of trunk, *o*, depressor, *p*, left vagus (inhibitory), *q*, superior cardiac nerve (accelerator), *r*, branch of superior laryngeal to superior cardiac, *s*, middle cervical ganglion (accelerator), *t*, inferior cervical ganglion (accelerator), *u*, deep cardiac plexus, *v*, superficial cardiac plexus, *w*, left posterior pulmonary plexus, *x*, left coronary plexus

The incision was made along the sternocleidomastoid muscle and the relations shown in Figure 3 were made out



Stimulation by faradic current of the vagus caused severe pain in the breast, faradization of the fibers known as the depressor caused slight cough but no alteration of the pulse. Blood pressure varied from 120 to 145 systolic and from 75 to 105 diastolic, mounting steadily toward the end.

Following the operation, the patient had dyspnea and complained of air hunger. Edema developed, the heart dilated. There was no further angina. He died fourteen days after the operation with heart insufficiency symptoms.

Odermatt is not certain what was cut in the operation.



Fig 3—*a*, sympathetic of neck, *b*, hypoglosseal, *c*, branch of hypoglosseal, *d*, vagus, *e*, laryngeal superior, *f*, and *g*, the two roots of depressor

Dr S W Ranson (Northwestern University), whose studies and comments on this work have been most helpful, is of the opinion that the good results in Wenckebach's <sup>4</sup> patients were due to the fact that Hofer, who operated on them, cut the superior cardiac branch thinking it was the depressor. There is still one other theory worth setting forth, and that is that there are connections between the superior cervical ganglion and the two ganglions of the vagus, as well as with the superior laryngeal, and in removing the cervical ganglions some important bypaths are interrupted which contribute to stabilizing the first part of the aorta and the coronaries. This does not make the situation any less complex, and we will now review the operations on angina published to date and

reported to us by letter, in the final attempt to show that the chief result in all the proposed and executed operations has accomplished only what has been accomplished in a large majority of our cases and patients operated on by our procedure

#### REVIEW OF THE LITERATURE

The operative procedures to date are divided by Kappis<sup>8</sup> into five groups

1 Resection of the middle and lower cervical and upper thoracic sympathetic ganglions on the left side Three operations, two by Jonnesco<sup>1</sup> in syphilitic men, aged 38 and 54, respectively, and one by Tuffier<sup>9</sup> in an arteriosclerotic man, aged 50 In all, the anginal attacks were relieved

2 Resection of all three ganglions of the left cervical sympathetic chain and the upper thoracic ganglion Bruning,<sup>10</sup> Kummell and Kappis<sup>8</sup> each operated on women, aged about 60 years Bruning and Kummell's cases were rendered free from attacks Kappis' case, a woman, aged 62, with increasingly severe attacks of pain in the heart region and left arm, whose blood pressure was 200 systolic and 170 diastolic had an attack during the operation Four months after operation, after exertion, attacks of pain began again behind the lower sternum and in the back Accompanying this also was a feeling of anxiety

In this connection must be mentioned a brief report by Pleth of Stockton, who claims to have done the Jonnesco operation on four patients with angina, with relief of pain One died of aspiration pneumonia The published report is without detail

3 Resection of the main trunk and superior cardiac branch of the superior cervical ganglion Five cases were reported by us, one patient died six hours after operation

4 Severing of the "depressor vagi" Eppinger in Wenckebach's clinic reports five patients operated on by Hofei, two on the left side alone, and three on both sides, one died and the others were relieved Odermatt<sup>7</sup> reports a sixth patient who died in thirteen days of progressive heart insufficiency

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8 Kappis, M Diskussionsbemerkungen zu, Das Schmerzproblem der Eingeweide, XLVI Kong d deutsch Gesellsch f Chir, 1922, Arch f klin Chir **121** 188, 1922, Med Klin **19** 1658 (Dec 23) 1923

9 Tuffier, T Diskussionsbemerkung, ref Bull de l'Acad de med, Paris **86** 99 (July 26) 1921

10 Bruning, F Die operative Behandlung der Angina Pectoris durch Exstirpation des Hals-Brustsymathicus und Bemerkungen über die operative Behandlung der abnormen Blutdrucksteigerung, Klin Wchnschr **2** 777 (April 23) 1923, Arch f klin chir **126** 490, 1923



5 Severing of the "depressor vagi" and extirpation of the lower half of the left superior ganglion to the lower half of the middle ganglion Borichard<sup>11</sup> reports such an operation on a man, aged 54, who, except for a light attack on the fifth postoperative day, was relieved. He died, three weeks later, of acute circulatory disturbance in the brain.

To these groups should be added a case reported by us (Case 2) of dextral radiations of pain, in which a resection of the right superior cervical ganglion was done with complete relief.

6 We now add nine cases, in which the operation consisted in removal of the superior ganglion, one of them just referred to and one where the ganglion removal followed a year and a half after simple section of the left trunk and superior cardiac branch. Of these one patient died as a result of the operation and one two weeks later. The others have been relieved, except Case 6, and he has been relieved of all but the referred pain and pain due to trauma of operation.

To this group are added brief reports of cases by Bacon, Holmes, Naftzinger, Lambert, Marvin (two cases) and Mortensen. The patients were all relieved of the substernal agony and with but one disturbing complication (Marvin's first case). Other successful operations have been done but the results were not published, and reports of them were not available to us.

#### REPORT OF CASES

CASE 1—H S H, a man, aged 54, entered the hospital on Sept. 19, 1922. The entrance diagnosis was angina pectoris.

*Present Illness*—The patient had lower third substernal discomfort and some shortness of breath for the last few years. For the last few months the condition had become more serious. On the least exertion he had pain in the center of the chest and epigastrium, which eating exaggerated at times (from one-half hour on). He did not vomit, but belched at times. The pain radiated to shoulders and arms, and he had numbness and tingling in the hands. The pain passed away in from five to ten minutes, and went faster if he assumed an erect position. The attacks of "distressing pain" under the lower third of sternum began fully two years ago. They occurred as an incident to excitement or muscular effort, and consisted of a painful feeling of pressure, which would extend upward across the upper chest and into the back between the shoulder blades, and recently down the arms where it consisted of an ache in both arms and upper forearms. There was also numbness, tingling and pain in the fingers, but no neck pain. The pain was equally distributed to the two sides. These attacks would come four or five times a day, growing more frequent as time went on, and following less exertion. Once in a while he awoke with an attack the usual duration of which was from five to ten minutes. Belching might relieve an attack, and soda seemed to help. A nitroglycerin tablet relieved in a few minutes. Standing up seemed to help always. The attacks did not vary much in severity or duration. Shortness of breath marked the condition in the beginning. The patient lost 25 pounds (11.3 kg) in the last three months. His average weight for twenty years was 210 pounds (94 kg). He dieted last May and lost 20 pounds (9.0 kg). In April, 1922, the attacks became

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11 Borichard, quoted by Kappis, Footnote 8

more severe, the pain extending down the arms for the first time. The first severe attack followed running for a car. The patient had no sense of "impending death" in any attack.

In spite of diet and nitroglycerin and more control of effort, attacks continued. Shortness of breath did not bother him recently.

*Family History*—Negative

*Past History*—He had not smoked for two months. He ate regularly and his appetite was good. He ate only two meals a day, and slept fairly well. The bowels were normal. He had nycturia three years ago, and had had measles and mumps. He did not have malaria or typhoid. The patient denied venereal history. He has had no rheumatism or gout and never underwent an operation. He has never had any injuries.

*Physical Examination*—The general appearance was of a well nourished man, with rosy color, the size and shape of whose head was normal, the eyes clear, pupils equal and regular and reacted normally. The nose was normal. The hearing was good. The mouth and teeth were fair, some teeth were crowned, the membranes were normal and the throat negative. Partial tonsils were still evident. In the chest the breath sounds were roughened.

*Heart*—Blood pressure was 108 systolic, 62 diastolic, the sounds were not loud owing to the thick chest wall, there were no discrepancies and no irregularity, the pulse was full, regular and compressible.

*Abdomen*—There were no masses, tenderness or rigidity. The genitalia were normal.

*Reflexes*—The knee jerks were normal. On September 20, the blood pressure was 108 systolic, 62 diastolic. September 22, the patient had no pain since he entered hospital because he has been kept (1) at rest, (2) on light diet, (3) on digitalis and sodium nitrite for the last twenty-four hours.

The patient recognized the connection between his pain and physical effort. The nitrite was stopped on account of the absence of pain and low blood pressure, 108 systolic, 60 diastolic.

*Urimysis*—Amber, clear, specific gravity, 1.015, alkaline, no albumin, no glucose. Microscopic examination showed very few amorphous phosphates, few red blood cells and mucous threads.

*Gastric Contents*—Test meal. The amount obtained was 105 cc, normal in character, the total acidity of which was 59, free hydrochloric acid 52.

*Wassermann Report*—Negative

*Fluoroscopic Examination*—Showed a thickened dilated aorta. The aorta almost filled the postcardiac space. There was considerable hypertrophy of the left ventricle.

September 23, the pulse was 54. Blood pressure, 114 systolic, 60 diastolic. The patient had slight pain before breakfast in the morning, which lasted for a few seconds. September 25, the patient was still on digitalis. The pulse was 68. There was no pain. The blood pressure was 114 systolic, 56 diastolic. September 26, roentgenograms, taken from the lateral and from the antero-posterior, showed considerable thickening of the aorta, also some dilatation. Both diaphragms were irregular, especially the right. Heavy peribronchial thickening, also hilum thickening was seen in the chest.

*Conclusions*—Considerable radiologic evidence of aortitis.

September 27, the patient had no pain and was given one week's leave. October 4, he returned in the morning. He noted slight pain whenever he made any special exertion, such as taking a three-block walk, or went upstairs at all fast or carried a grip.

The patient woke up with pain at midnight a few nights before, he had eaten a fairly good dinner. He was not constipated. His weight the morning of return was 182 pounds (82.6 kg), a gain of 2 pounds (0.9 kg) in a week. The blood pressure was 111 systolic, 56 diastolic. The pulse was 72.

October 5, electrocardiogram showed the T wave inverted in Lead I. The vital capacity was 3,760 c c, about 80.5 per cent of the normal height standard.

October 6, the weight was 181. The patient had pain in the morning, caused by rubbing himself with a bath towel. The pain passed away when he stood up. The blood pressure was 122 systolic, 64 diastolic. The pulse was 62 and regular. The patient was taking no medication.

October 11, operation was performed for the resection of branches (cardiac and trunk) of the superior cervical ganglion, after  $\frac{1}{6}$  grain morphin,  $\frac{1}{180}$  grain atropin, nitrous oxide and ether anesthesia. The duration of the operation was forty-five minutes.

The pulse was 88, respiration 20, the patient's color was good. The pupils were contracted. He was perfectly conscious one hour later, and complained of pain in the chest two and one-half hours later. The pulse just before this was good. The patient vomited five minutes later and appeared to be choking. The intern administered epinephrin and later camphorated oil, followed at once by oxygen as the color was pale and the pulse imperceptible. The patient died a few minutes later, twenty minutes after the vomiting began. Necropsy was refused.

This was regarded as a cardiac death, and believed to be referable to serious coronary sclerosis and myocardial disease.

CASE 2—J. D., a man, aged 68, entered hospital with marked cardiac decompensation, auricular fibrillation and dyspnea, after three months of care at home following a severe attack of angina.<sup>12</sup> Several mild attacks a day were the rule, and in the three months interval three severe attacks had occurred.

The pain was under the upper sternum and the radiations were dextral, except in the first attack where they extended to both arms. The right superior cervical ganglion was removed by Dr. W. B. Coffey, with complete cessation of both the severe and minor attacks.

The negative T wave in Lead I before operation was not visible after the operation.

CASE 3—P. I. M., a man, aged 41, Danish, a boiler-maker, was admitted to the Southern Pacific Hospital, April 23, 1923. The diagnosis was angina pectoris, with the complication of aortitis.

*Family History*—Negative.

*Past History*—Negative.

The patient was married and had one child. He denied venereal history.

*Complaint*—The patient had pain over the heart on slight exertion for the last two and one-half months. He got wet while at work, and had a mild form of influenza on February 7, and immediately afterward he noticed shortness of breath, and a few days later noticed pain in the precordium after exertion. In two weeks the pain was severe enough to confine him to bed. This pain first started just under the left of the sternum about at the level of the eighth rib, and immediately traveled up to the neck and out both arms, stopping at the elbow usually, and always on the inside of the arm. This pain in the first attack lasted for about thirty-six hours. Since that he has had attacks lasting for only a few minutes. The pain in these attacks did not travel down the arms but did go up to the neck. These minor attacks came on after eating heavily, slight exertion and excitement.

For two months (since February 16) he had been laid up. He had what he called "flu." His average weight was 206 pounds (92 kg.) now 185 (83.9 kg.).

*Physical Examination*—The patient appeared healthy in all respects, except for a purplish flush on his face, which was most noticeable on the lips. The head showed no abnormalities. Blood pressure, 125 systolic, 85 diastolic. The

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<sup>12</sup> Brown, P. K. Cervical Sympathectomy for Angina Pectoris. Report of a Case with Dextral Radiations of Pain, J. A. M. A. 80:1692-1693 (June 9) 1923.

pulse was slow, 66, regular and appeared normal. The heart was slightly enlarged, the tones faint, with slight systolic roughness over the aorta. There were no irregularities of rhythm.

The abdomen was negative. The extremities were normal. The reflexes, normal.

April 24, the blood pressure was 100 systolic, 76 diastolic.

*Urmalysis*—Negative.

*Blood Report*—Hemoglobin 90. Erythrocytes, 5,040,000. Color index 9. Leukocytes, 5,000.

April 26, the Wassermann test was negative. Vital capacity, 4,050, 96 per cent.

*Roentgen-Ray Examination of Heart and Aorta*—The entire left chest was obscured by a faint opaque shadow. Interfissural thickening had taken place on the right side. The aorta was broadened. There was general hypertrophy of the heart muscles.

*Conclusion*—Arteriosclerosis of the thoracic aorta, and general hypertrophy of the heart muscles. The opaque shadow seen on the left side could be due to congestion, however, it was more reasonable to believe that a chronic pleuritis had taken place on this side.

May 3, the patient still had some pains. There was a subacute inflammation of the entire vocal box. There appeared to be some inhibition in movement of the left vocal cord.

Electrocardiogram showed left ventricular preponderance and some indication of a negative T wave in Lead I.

May 17, the patient was dismissed somewhat improved.

June 11, he was readmitted to hospital, after two weeks' leave, because of persistent attacks of pain and inability to work.

The patient stated that since he left the hospital he has had daily attacks of pain in the precordial region, without any radiation. During these attacks he felt as if he were suffocating.

June 12, the blood pressure was 134 systolic, 96 diastolic.

June 21, the patient was taken to the operating room at 9 30 a. m. The anesthetic of nitrous oxid and ether was started immediately. When the patient came to the surgery he was in a highly nervous state. At 9 40 he began to go into what appeared to be a collapse. His pulse became very weak, in fact hardly obtainable and irregular. We were unable to hear any heart sounds. His breathing became very irregular, slow and shallow. The color of his face became very peculiar, the left side was blue in one portion and pale in another, there being quite a marked distinction between these two areas. The right side of the face had a grayish pallor. He looked like a dying man.

The anesthetic was stopped, and 3 cc of camphorated oil was given him hypodermically. In about five minutes his condition became better, the heart and pulse were fairly good, and the ether anesthetic was continued.

The operation was begun at 10 05 and ended at 11, with the closing pulse 84, respiration 20 and the color fairly normal. The left superior cervical ganglion was removed by Dr Coffey.

June 22, the patient complained of sore throat and spoke in a whisper. He had a temperature of 101. The pulse was 100.

June 23, he had no pain in the precordial area or shoulder since operation, and said he felt fine. He still complained of sore throat. The temperature was 101. The patient was kept on a liquid diet.

June 24, he was able to speak a little louder. The sore throat was still present.

June 25, the patient spoke better. The sore throat was disappearing. Blood pressure, 130 systolic, 92 diastolic, in both arms.

July 2, he had a desquamative dermatitis on the right leg before operation, and this spread all over his body and on the fingers and palms, not on his feet.

or face. He complained of numbness in the left side of the face, hoarseness and cough, and said his tongue was in his way and that he could not chew without biting it. The blood pressure was 110 systolic, 80 diastolic.

July 9, the patient had no pain whatever and felt better than at any time since the operation. The hoarseness continued, also the difficulty with the tongue. The cough was better. The dermatitis was practically gone. The blood pressure was 135 systolic, 110 diastolic, and the patient was discharged.

August 17, he was readmitted to the Southern Pacific Hospital, with the admission diagnosis of brachial neuritis (traumatic). The patient was given hot magnesium sulphate compresses, with steady improvement.

August 27, he was discharged relieved, by the last report on March 10, 1924, there was no subsequent trouble.

CASE 4—E. H., a man, aged 28, entered hospital June 6, 1923, with the diagnosis of angina and mitral stenosis.

*Family History*—His mother had high blood pressure at the age of 46, and his father had asthma.

*Previous History*—No history of rheumatism or tonsillitis. He had pleurisy in 1917, otherwise his history was negative. The patient was married, and had three children.

*Present Illness or Injury*—On May 5, at 7:30 a. m., after breakfast, the patient had pain in the region of the heart apex which got steadily worse, extending first to back of left side of neck, then across base of heart under the sternum where it stayed for one hour. The whole attack lasted for two hours. If he took a deep breath, the pain was worse and the heart beat rapidly. He had not worked since then by his physician's orders. The second attack was on the afternoon of May 8, at 3 p. m. There were two or three waves of pain, chiefly in the heart region. It was not in the shoulder or neck or substernally as before. The pain lasted off and on until 8:30 p. m. The patient took a good deal of medicine.

*Teeth*—One crown but otherwise they were in good condition.

*Chest*—No signs of a pathologic condition.

*Heart*—The sound was very weak, systolic murmur loudest and roughest at apex, which was in the fifth space at the mammary line. The second pulmonic was accentuated.

May 11, at breakfast the patient had a weak spell and felt as though he would faint, and had to go out and sit down. He became dizzy but did not faint. The heart pounded but did not hurt. He had an ache in his back, in the lumbar region, which developed May 10.

May 12, he had a dull ache in the heart region and left arm the previous night from 4 p. m. until he went to sleep.

May 16, when the tube was passed to remove a test meal, the patient had an attack of angina, with pain radiating down the arm and down the outer side of the left leg. The arm pain was worse than the leg. He had pain May 15 in the back of the neck.

May 19, the patient had pain again on the previous night, not severe, but felt it in the left arm.

May 21, not much pain May 20, but two or three pains in apex region after going to bed.

May 22, pain in heart May 21, at night, caused by vomiting after a dose of castor oil. At 10 a. m. the patient was in operating room. The pulse was 60 and regular. Blood pressure, 120 systolic, 50 diastolic. Left superior cervical sympathetic ganglion removed.

May 23, the patient vomited in the morning but had no attack of pain associated with it, either in chest or arm. The left pupil was contracted and the left lid drooped slightly. He said he had once felt as if a bee was buzzing in his pocket over his heart, but had no pain whatever in the heart. There was irritation of the recurrent laryngeal, and the patient had trouble swallowing.



There was pain in the head over the left eye the previous night from 11 p m on, which he still had at noon He swallowed better than on the previous day He said his eye felt funny and half closed It was sore to the touch or when he moved the eye He had a slight conjunctivitis in that eye Ether (?)

May 26, the patient had nightmare (dreamed he fell in a river) during the night and awoke with violent pounding of the heart, which he says shook the bed and caused him a panicky feeling but no pain He swallowed without trouble There was slight ptosis of the left eye lid The left pupil was smaller than the right

May 27, suddenly, yesterday afternoon, while lying quietly in bed, he had a buzzing feeling over an area the size of a dime just inside the left nipple Two or three minutes later, he had a pain (dead aching in character) which differed from the former acute shooting pain It was quite severe, extended to the top of the shoulder joint and down the inside of the left arm and down to the wrist The fingers felt a tingling only, as if asleep The pain lasted from five to ten minutes and gradually wore off He moved about in bed, and a little later took his supper and later took soda and got rid of a good deal of gas The pain, however, had gone Later he described it as a gas pain He was a good bit apprehensive and might have been frightened by the attack and exaggerated it, but he certainly had symptoms of an anginal attack

May 31, the left conjunctivitis had about disappeared, but after reading it returned and he had pain in left supraorbital region The contracted left pupil followed the left cervical sympathectomy The patient was referred to the oculist, Dr Blake for recommendation

June 1, the eye was examined by Dr Blake, with the following report The left pupil was smaller than the right The reaction to light and in accommodation was normal Miosis was probably due to absence of tonic dilator impulses by way of cervical sympathetic The fundus was normal in both eyes Yesterday afternoon, while playing cards, he had a sudden feeling of oppression when breathing, his head was light and he had a choking sensation He found he could breathe easily but felt the need of air He felt faint and dizzy He came back to the ward, his legs felt weak and his head felt as if he were floating on air Took 2 drops of nitroglycerin and in thirty minutes was quite recovered He lay down during this time There was no immediate effect from the nitroglycerin The nurse's record said immediate relief, but he had been getting better for from ten to fifteen minutes before the nitroglycerin All functions of the body were being performed well, although a laxative at night had been used Blood pressure was 110 systolic, 66 diastolic The pulse was 60 The electrocardiograph showed only right, ventricular preponderance

June 4, examination (P K B) could not detect the slightest heart murmur There was a reduplication of the first tone at the apex The rate and rhythm were normal There was nothing to indicate a valve lesion Blood pressure, 110 systolic, 60 diastolic Pulse, 68

June 26, the patient still had a slight numbness in front of the left ear, and below it to just below the angle of the jaw He was sore over the region of the lower parotid, and eating sour things caused pain There was nothing found in the teeth, but both tonsils were big, cryptic and infected He caught a cold which lasted for four or five days, and was pepless for a time He was feeling well before that Blood pressure, 106 systolic, 60 diastolic Pulse 88 Tones of the heart seemed absolutely normal There was no change in size Except for gas, he had no complaint, and when he had a great deal of gas, or over-exerted, he had an ache with three or four successive heart beats, which lasted intermittently for half an hour This continued until relieved of gas, and was worse when he was without food for longer than usual Eating then relieved him, because he belched as soon as he had eaten

CASE 5—A W B, a man, aged 58, with a history of angina, was admitted to hospital on the service of Dr Earl Greenwood, Aug 3, 1923 The patient's chief complaint was pain in the precordium extending down the arm, lasting for the last nine or ten years

*Past History*—The patient was an inveterate smoker, a heavy drinker (not for the last four months) and a heavy eater. He had had measles and mumps at 17, with testicular involvement. About ten years ago, the patient had a severe attack of pain in the right upper quadrant, gallstones and no jaundice. He has had some urinary disturbance, with frequency at night, which has diminished lately since letting up on coffee, there was no burning on urination. Questionable primary syphilis, no secondaries.

*Present Illness*—Nine or ten years ago the patient first noticed the onset of pain in the precordium following some exertion, of a dull aching type, periods of freedom occurring nearly every day. Attacks were brought on by cold air, anger, excitement or effort.

About one year ago, the patient undertook extra work involving nervous as well as physical strain. At this time the pain, of a sharp shooting type, became more severe, radiating down the left arm. The patient was not certain whether the pain originated in the precordium or the left arm, but both are associated. He stated that there was an area over the second rib painful to touch during attacks. There was no substernal pain. The patient has had five severe attacks during the last five days. During examination, he had a long attack lasting several hours, relieved after five doses of  $\frac{1}{100}$  grain nitroglycerin hypodermically. He had been in the habit of taking large amounts of black coffee for the last year. He had been an inveterate smoker all his life. On the day of admission he used a considerable amount of alcohol in an effort to relieve the pain. He has had some shortness of breath lately but no swelling of the feet or ankles and no asthmatic attacks.

*Physical Findings*—An elderly man, of florid complexion, and somewhat cyanotic was seen. The pupils were irregular and small (cotton?) The teeth were in a very poor condition, the gums were discolored. The neck showed some pulsation in veins. The chest was thick, there was some dulness over the whole area and both lungs, especially at bases, elicited musical coarse râles, there was a small area of pleuritic rub in the right axilla posteriorly. The heart area of cardiac dulness was enlarged to the left 2 cm outside the mid-clavicular line, the sounds were rapid and weak, with a faint systolic murmur at the apex. Blood pressure, 148 systolic, 100 diastolic.

*Abdomen*—Protuberant. The liver was enlarged about one finger below the costal margin, somewhat tender, otherwise physical examination was negative. The Wassermann test was negative, and the urine was negative.

Roentgen-ray examination of the thorax showed "myocardial type of heart," some widening of the aorta, increased bronchial tree markings about the hilum, probably secondary to cardiac trouble.

August 9, the blood pressure was 138 systolic, 28 diastolic, August 10, 122 systolic, 80 diastolic, August 12, 118 systolic, 80 diastolic.

August 15, left cervical sympathectomy was performed. The anesthetic began at 12 25, the operation at 12 40 and ended at 2 p m. The superior cervical ganglion was removed. The superior cardiac nerve and main trunk were resected. The pulse before operation was 88, after 110. Respiration, 19 before, after 28. Blood pressure just after operation (2 p m) was 90 systolic, 70 diastolic. At 8 p m it was 118 systolic, 78 diastolic.

August 16, the blood pressure was 112 systolic, 76 diastolic. The patient complained bitterly of pain in the left side of the neck and begged for relief. Nitroglycerin,  $\frac{1}{50}$  grain hypodermically and  $\frac{1}{50}$  grain by mouth, gave no relief, even repeating both doses. The pain he complained of seemed to be local, due to trauma of operation. He had no arm pain, which had been his worst symptom, till reminded of it at 8 p m.

August 17, the blood pressure was 112 systolic, 70 diastolic, August 18, 93 systolic, 58 diastolic, sitting up, August 19, 118 systolic, 76 diastolic, August 20, 110 systolic, 72 diastolic, 128 systolic, 86 diastolic, lying down, August 21, 118 systolic, 74 diastolic, sitting up.

August 23, urine analysis, reaction, trace of albumin, specific gravity 1.015, occasional granular casts, many hyaline casts, no sugar

Within the week after operation, he was up and walking to the sun porch. His chief complaint was air hunger. He had fair nights on phenobarbital, 2 grains. His limbs began to swell within a few days of operation, the urine became less in spite of a diuretic every two hours. The pain was chiefly in the neck, but he complained at times each day of pain above the heart and in left forearm. A troublesome cough developed on the fifth day after operation, and the dyspnea grew worse. In spite of improvement in renal output, daily bowel movement, light diet and abundant stimulation, the heart from this point failed steadily and the dyspnea grew worse.

The patient died at 9 p. m., the tenth day after operation. During the last five days his one complaint was air hunger, and except for one attack of heart pain relieved by aromatic ammonia, there was no true angina. Necropsy was refused.

**Clinical diagnosis.** Advanced coronary disease with interstitial myocarditis. Death from failure of the heart.

**CASE 6**—A K, a man, aged 59, on Oct. 3, 1923, complained of upper substernal pain and flatulence off and on for the last three weeks. The pain came on after exertion and the attacks lasted for ten minutes, the patient having to sit and gasp for breath. Eight years ago he ran for a train and got out of breath, fell and could not speak for twenty minutes, so severe was the pain. The pain was located in the mid-chest across sternum, and generally shot from the elbow down to finger tips without affecting the shoulder or upper arm. No other radiation of pain was noted. Dyspnea accompanied the attacks. These come on an average of from six to seven times daily. There was no pain when in bed and quiet. There was a good deal of bloating and flatulence, which aggravated the chest pain. There was no dizziness. The disappearance of chest pain left him with a frontal headache. Cold sweat followed the attacks.

The pain began when he made the exertion eight years ago. He thought it was in the bronchial tube and throat, on account of the difficulty in getting his breath. Three years ago, in the Siskiyou Mountains, he had recurrence of the pains, and difficult breathing which became normal when the pain disappeared. The blood pressure was 118 systolic, 70 diastolic.

October 5, the patient had an eye examination. The external eyes were negative. The mediums were clear. The fundi were negative. Myelinated nerve fibers were present at the margin of the disks in both eyes.

Roentgen-ray examination of the chest, heart and aorta showed considerable hypertrophy of the left ventricle. The aorta was increased in density. The transverse portion of the arch measured 7.5 cm., which is a normal measurement. The heart measured 15 cm. in the transverse diameter, 17 cm. in the diagonal diameter. **Conclusion.** Aside from the unusual density of the aorta, no pathologic findings were seen.

October 6, the patient had no attacks of pain on October 4, but had two attacks October 5, one at 4 p. m., lasting from five to ten minutes, one at 8 p. m., lasting from three to four minutes. At 4 a. m. he was awakened by an attack more severe than usual and lasting for ten minutes. He took no medicine, and perspired freely after the attack. He had no special trouble with breathing, but in this attack he felt that he must draw in a long breath. The pain was always located below the upper sternum and ran over toward the upper axilla. Sometimes the pain shot down the forearms, and that morning especially he felt it in the right forearm, it seemed to terminate in the thenar eminence. It did not radiate to the neck, but did at times radiate to the left shoulder, never to the right. Never in the back of the head, but when the pain (substernal) had lessened he had a frontal headache for from twenty to thirty minutes. The vision was never disturbed. The patient has had "touches of pain before in the right forearm." Nitroglycerin,  $\frac{1}{400}$  grain, was prescribed for attacks. The blood pressure was 138 systolic, 98 diastolic.

October 8, at 8 p m the patient had an acute attack of pain in the sub-sternal region, radiating to the back between the scapulae to both arms. It was not relieved by two doses of nitroglycerin at one-half hour intervals. There was slight relief from amyl nitrite.

October 9, he had had anginal attacks during the night, and pain off and on all night. He was given nitroglycerin, amyl nitrite and morphin. He vomited the food this morning that he had eaten the previous afternoon. He had eaten marshmallows before supper.

October 11, roentgenogram of the chest showed opaque shadow at the left base, probably due to slightly thickened pleura. The stomach filled in the usual manner, and was normal in outline, size and position. No filling defects were seen. Roentgenograms of the gallbladder showed a rounded shadow under the liver. The stomach was empty in the usual six hours time. A twenty-four hour examination showed the colon well outlined.

The findings were marked spasm of the pylorus and bulb, in conjunction with the round shadow under the liver pointed to a condition of chronic cholecystitis.

October 13, the patient had no pain since October 8.

October 14, he had an attack the previous night, relieved by nitroglycerin.

*Family History*—Negative.

*Habits*—The patient did not smoke or drink.

*Past History*—Hemorrhoidectomy in 1916. Otherwise negative.

*Examination*—A well developed, middle-aged man lying quietly in bed, in no apparent pain was seen. The head, eyes and nose were normal. The mouth had plates. The tonsils were negative. The chest was symmetrical, with normal expansion. The lungs were resonant throughout, there were no adventitious sounds. The heart apex beat was best heard in the fifth intercostal space nipple line. The sounds were distant and regular, there was no murmur. The abdomen was negative. The extremities were negative.

November 12, the patient returned from leave of absence (thirty days). The usual symptoms were present. Some days he would have from three to four anginal attacks, others were free from pain. The slightest exertion brought on an attack of precordial pain radiating down the left arm. There was shortness of breath during the attack and the patient could not breathe. Also cold sweat appeared. The patient had a slight postcervical ache. He had not become any better or any worse.

November 13, on ascending an incline yesterday, he had to stop twice on account of heart pain. Vital capacity 2,800 c c. The blood pressure was 100 systolic, 72 diastolic.

November 14, the electrocardiograph was made yesterday. The patient had no attacks. For the last month he has had no day without attacks, from two to six a day, depending on exertion. These attacks were relieved with nitroglycerin. Tincture of digitalis, 20 drops three times daily was prescribed.

November 15, there was an abrasion on the right side of the epiglottis but no evidence of any bone in the larynx or upper trachea.

November 17, the blood pressure was 116 systolic, 80 diastolic.

November 19, the left superior cervical ganglion was removed, under local anesthesia, by Dr Coffey.

November 20, the operation produced no reaction in the patient. After the wound was closed, the blood pressure was 118 systolic, 78 diastolic, and the pulse 68, regular and full.

During the operation the patient experienced a pressure pain above the mid-clavicular region over to side of larynx. When the superior ganglion was grasped with forceps, he felt the same pressure pain at the base of the brain. (Distinctly not the burning pain as described by H., the other patient done under local anesthesia.) He had blurred vision in the left eye in the morning.

He had no numbness at angle of left jaw, which all the other patients have described. Early on the afternoon of November 19, the patient had a pain in the left breast region lasting for ten minutes, unlike any pain he had had before. He thought it was in his heart. It did not radiate to the neck or arm. The patient stated that he was very glad he had the operation done under local anesthesia, that the pain at no time was disturbing and was only momentary. He said he would be willing to go through it again the next day if necessary.

November 21, the patient had been feeling well all day until 4 p. m. when he developed slight pain down the left forearm. The pain lasted for one hour, and was just like attacks in the arm before operation. There was no substernal or precordial pain. There was slight numbness over the left angle of the jaw, otherwise he was feeling all right. There was a slight bowel movement, as cascara had been given.

November 23, the patient was up, November 22, for three or four hours. He had slept well the previous night until 3 a. m. He awoke with pain in the region of the apex of the heart, which extended all over the precordial region along the wound and up to the left temple region. He felt it in the left eye also, and down the whole left arm, especially in left forearm flexor surface as far as wrist. The pain lasted for thirty minutes. He was given  $\frac{1}{150}$  grain of nitroglycerin hypodermically, with relief in ten minutes. The patient stated his evening meal was the ordinary diet. He felt no discomfort following, and slept until 3 p. m., when he was awakened by a pain in the epigastrium (as far as the umbilicus) which extended up the sternum to the neck. It was unlike any pain he had experienced during his previous anginal attacks. However, he stated there was an associated pain over the heart extending up to the neck and eye (left), to the wound and down the left arm and forearm, similar to the previous anginal attack. The pain was quite severe, and he felt like vomiting during the attack. The patient thinks this attack was due to indigestion. He had been given cascara and mineral oil the night before, and this was followed by some epigastric distress. In addition to this, he had a decided impression of fear, due to the fact that a week before an anginal patient had died after being six hours in the ward in an attack, and the afternoon before, another heart patient came in, in a state of collapse, after being allowed to dress and take a short walk. The patient went to bed at once, saying he didn't want anything like that to happen to him. These facts are recorded, together with a notation of digestive disturbance, for what value they may have in connection with the nervous origin of attack.

November 24, at 6:35 p. m., the patient suddenly was seized with sharp pain about the sternum, also beneath the lower end of the body of the sternum, also pain over the heart, which did not radiate to the neck or shoulder, but was quite agonizing from the elbow down. The patient also complained of pain about the mastoid, a sensation similar to that of earache. This entire attack lasted only for five minutes after taking 2 drops of nitroglycerin. Profuse sweating of the lower extremities followed. The blood pressure was 128 systolic, 90 diastolic (Tycos) during the attack. The patient described the attack as "light" compared to some he had had. The left pupil was contracted and the left upper lid drooped slightly.

A three weeks' leave of absence was given the patient as he had a marked suggestibility and it was quite impossible to evaluate his symptoms.

December 19, the patient returned complaining of (1) a dull aching over a small spot in the center of the left shoulder toward the back, (2) pain at the angle of left side of jaw on beginning to chew, for three or four movements of the jaw. This began about December 1, and continued since. The patient did not notice anything but numbness at other times, (3) pain and tenderness over a small area over the left anterior occipital region about the level of top of ear, (4) on December 7, 8 and 16, he had pain around a small area over the heart apex, which worked back under the shoulder blade instead of to the front as

formerly He took nitroglycerin once with relief Again, on December 18, when returning to San Francisco, the patient, while carrying a bag, hurried, and had another attack Exertion had been a factor in each attack

December 22, the blood pressure was 118 systolic, 76 diastolic

December 24, at the eye examination it was found the right pupil was larger than the left, both reacted to light and in accommodation The left eye slit was narrower than the right The muscle movements of both eyes were good

December 26, on the night of December 23, at 7 p m, the patient had pain in the neighborhood of the left nipple over an area of 10 cm across He had a cramp in the flexor surface (lower third) of the left forearm, which was relieved by nitroglycerin The cardiac pain did not radiate The patient did nothing unusual except eat a hearty supper at 5 p m He was in bed when the pain began He was taking pyramidon  $2\frac{1}{2}$  grains for pain below the left ear, anterior to operation wound and extending up in front of ear The ear pained only when he began to eat The neuralgic pain up behind the ear did not recur after he took the two doses of pyramidon, grains  $2\frac{1}{2}$ , at 8 a m and 5 p m

December 27, at 7 35 p m, the blood pressure was 122 systolic, 86 diastolic The patient stated he was suddenly seized with severe aching pains over the precordium, also cramp-like pain in the left wrist, and extending about 5 inches (12.7 cm) up the left forearm There was no radiation of pain to neck, shoulder, or to mastoid process There was no substernal pain Nitroglycerin,  $\frac{1}{100}$  grain The attack lasted about three minutes

December 29, the patient had three attacks December 28 The first was while wandering around town going up a hill, he had pain only in apex of the heart and none in the arm, second one while walking, not hurrying, third one while in bed at 7 30 p m, two hours after eating

Jan 2, 1924, the patient had no attacks He complained of pain just in front of the lobe of the left ear and below the angle of jaw It was tender also to pressure, and worse when he began to eat At times he had it without eating

CASE 7—J B, a man, aged 59, a farmer by occupation, was referred by Dr O F Johnson, Dec 17, 1923, on the complaint of pain in the chest Three or four years ago, when walking one evening, he had occasional attacks of pain which began in the shoulder and extended down through the front part of the left arm to just below the wrist He did not feel it in the neck or head He felt it very slightly under the sternum at that time For three years, the attacks continued like this, with the chief pain in the arm They occurred only on exertion and from one to four times a month, and would pass off in a few minutes when he rested There was some dyspnea accompanying the attacks The patient never had any symptoms on the right side

About one year ago, without any known cause, he began to have some severe pain subinternally, occurring more frequently and lasting longer, never radiating to the neck or back of head

On admission, he felt the pain first across the lower sternum below the nipples and extending out nearly to them, chiefly in the center below the sternum The pain sometimes seemed to extend out beyond the nipples and sometimes a  $\frac{1}{2}$  inch (1.27 cm) below them He never felt it in the back except in the upper posterior part of the shoulder, and down the flexor surface of the arm to a point just below the wrist Sometimes it came without any exertion It seemed worse in cold weather

*Examination*—An obese Italian was seen whose blood pressure was 200 systolic, 118 diastolic

Heart rhythm was normal, the rate 60 The first tone was not very plain anywhere, the second was much exaggerated and ringing over the aorta, but there were no murmurs

Lungs There were no râles in the base of the lungs

The upper teeth were on a plate There were abscesses around the roots of the lower teeth

The tonsils were not unusual

The pupils were equal and reacted to light. The background was not visible because of marked contraction. The knee jerks were equal. He had had nycturia for the last six or seven years. Roentgenogram disclosed a shoe-shaped heart, marked hypertrophy and dilatation and a broadened aorta.

The Wassermann test was negative.

Electrocardiogram. Marked left ventricular preponderance, negative T wave in Lead I, vital capacity 3,100 or 83 per cent.

The urine was negative.

Operation under local anesthesia was done by Dr. Coffey, who removed the left superior ganglion. The patient smoked daily after the operation, and was discharged in eight days. He had a mild attack of appendicitis in this interval.

CASE 8—H. J. H., a man, aged 68, a purchasing agent, was seen Jan. 16, 1924, with an admission diagnosis of angina pectoris.

*Family History*—Negative.

*Past History*—He denied having syphilis or any serious illnesses.

*Present Illness*—The patient was told in 1910 that he had arteriosclerosis. He complained of headaches, vertigo and pain in sides of neck toward the back. This neck pain recurred in attacks for fully eight years before he began to have attacks of pain substernally, which radiated down the left arm. These attacks lasted only for a moment and were relieved by spirits of nitroglycerin, from one-half to 2 drops. The attacks were not very frequent, occurring about once a month, and according to the patient seemed to be brought on by worry only.

Since 1920, the attacks lasted longer, from about four to five minutes, and came on after any exertion such as walking from four to five blocks vigorously.

In 1922, the patient had pain in the base of the brain, and vertigo with the anginal attacks. The attacks always began with pain under the sternum, radiating across the chest and down the outside of the arm, only very rarely down inside of arm, sometimes entering the shoulder. The pain always went to back about to the level of the fifth dorsal in middle line. Occasionally, there was a slight pain in the back of the neck, which was not very severe and had not the same acute character. The patient did not smoke, and very rarely drank. Cold air did not provoke attacks. He might go for a few days without attacks, then have from one to four a day. For at least two months he has had two or more attacks a day, when he did have them.

The Wassermann test was negative.

The electrocardiogram showed slight ventricular preponderance.

Vital capacity, 2,550 c.c., 68 per cent.

*Screen Examination*—The heart was normal in outline, size and position. The aorta was considerably thickened, and measured 8.5 cm. in the transverse diameter, anteroposterior view. The heart measured 15 cm. in the longitudinal diameter and 12 cm. in the transverse diameter.

Roentgenograms, taken at 2 meters, showed the diagonal diameter to have been 15 cm. and the transverse 12.5 cm. The transverse diameter of the aorta was 6 cm. The antero-oblique position showed a marked thickening of the descending aorta, thus practically filled the posterior mediastinum.

*Conclusion*—Chronic aortitis of the thoracic aorta. Urine, negative.

During a week's rest in bed, patient had no severe pain and only a few slight pains.

January 23, notes made during operation, there was a systolic heart murmur with slight enlargement of the heart and broadening of the aorta. Local anesthetic was begun at 10:10 a.m. The patient was under considerable nervous tension, and in a cold sweat. At 10:35 he began having a slight anginal substernal pain. At 10:40 the pulse was regular, 120. Blood pressure, 220 systolic, 128 diastolic. One hour before operation the blood pressure was 178 systolic, 116 diastolic.

At 10 41 as the anginal pain still continued  $\frac{1}{75}$  grain nitroglycerin, 3 drops of a 1 per cent solution was given on the tongue. The pain disappeared in three minutes. The blood pressure fell so that the systolic could not be taken, diastolic was about 110.

11 10 After section of trunk and superior cardiac branch the blood pressure was 178 systolic, 100 diastolic. Pulse, 108. Contracted pupil.

11 15 Blood pressure, 165 systolic, 88 diastolic.

11 25 Pulse, 108.

11 35 Blood pressure, 162 systolic, 90 diastolic.

Pain in the middle of the left shoulder toward the back was felt when the branches of the cervical plexus were touched. This (Dr Coffey says) had nothing to do with the sympathetic system. In this operation, the cervical plexus was exposed for the first time.

January 24, the patient felt fine. One extra systole was noted. The blood pressure was 190 systolic, 120 diastolic. He complained only of a few short attacks of hiccough. His stomach was much upset January 23, and had not quite recovered. The breath was foul.

January 25, the patient had four attacks of hiccough in the night. He had no bowel movement the previous day. With the hiccough he had pain, each time he hiccoughed, from the midsternal region to the back. (Injury to phrenic or pneumogastric?) Compound spirit of ether was prescribed.

January 30, the patient had three attacks of hiccough on the nights of January 25 and 26, two the next night, one the night after and none since. The blood pressure was 146 systolic, 88 diastolic.

Feb 1, 1924. After walking about 400 yards yesterday, the patient lay down for a while and had a number of visitors, and with no known exciting cause had a moderately severe anginal attack at 6 p. m., quite like those he had already experienced, upper substernal pain going through to back between shoulders and slightly down the left arm. He took no medicine. The pain lasted for ten minutes and was not bad enough to cause him to think of medicine. The blood pressure was 172 systolic, 86 diastolic.

February 2, he had no subsequent attacks. His weight was  $139\frac{1}{2}$  pounds (63 kg.) before operation, in wrapper, 152 pounds (68.9 kg.) dressed. His tongue was clean.

February 22, Dr. Harry Weil reported the blood pressure was 129 systolic, 88 diastolic. The patient has had no attack of pain. He walked a block or two at a time and ate carefully. His feet became cold, but not more so than before. He had some swelling in the site of operation. The ear and shaved part of the face were numb. The left eye was inflamed, the lid drooped slightly, the left pupil was smaller than the right, though both reacted promptly to light. Every time he chewed on the left side, there was a single sharp severe pain felt in the molars in the upper left jaw. The second bite was free from pain. He might get it without chewing, and thought it might be caused by his teeth. But the regions in front of and behind the lobe of left ear and in the shoulder point were tender where Cases 1, 3 and 6 were tender. When seen May 15, he reported no further attacks. Exercises moderately.

#### CASES IN WHICH OUR METHOD WAS USED BY OTHERS

CASE 9—W. H., reported previously,<sup>2</sup> was the first patient operated on under local anesthesia, and the extent of the operation was severing the superior cardiac nerve and the main trunk of the left cervical sympathetic below the superior ganglion.

Following the operation in the early spring of 1922, the patient returned to his work as a bridge carpenter and continued well until November, 1923, when he was transferred to a job in the mountains at an elevation of 5,900 feet. He caught a severe cold, and in a few days developed a severe and sudden pain over the heart apex and in the upper left central epigastrium just under the ribs. The pain radiated to the left shoulder and elbow but not to the neck, nor



was it substernal in this attack. The attack was mild, but the pain continued for nine days with four or five intermissions a day. He was short of breath and had a disturbing cough, and night sweats on three occasions in the next ten days before entering the hospital. The pain differed from previous pain in not appearing in the neck, and in being especially severe in the region of the heart apex and in extending straight through into the back.

Examination revealed his heart was fibrillating. Blood pressure was 90 systolic, 70 diastolic. Wrist pulse, 144. There were râles in both apices (activation of old tuberculosis). On digitals, quinidin and strychnin the fibrillation ceased on the tenth day after entering the hospital. In this period, the patient had repeated attacks of angina always with the same distribution of the pain. The heart was found to be fibrillating in all the attacks that followed in the next five weeks, although the fibrillation was paroxysmal and of short duration. Fibrillation was not always present in attacks of pain. The patient remained continuously on doses of 2 grains of quinidin and  $\frac{1}{30}$  grain of strychnin three times daily. For the last ten days of his stay in the hospital, he complained of a severe burning feeling in the region of the heart apex. These were relieved promptly by nitroglycerin. The electrocardiogram showed the inverted T in Lead III, which was not present when the patient was first operated on in January, 1922.

Consideration was given to the operation on this patient suggested by Danielopolu and Hristide<sup>13</sup> and a complete study was made of the extent of the surgery necessary in this case and in Case 6. These authors suggest suppressing the principal sensory paths of the heart and aorta through resection of the posterior roots of the eighth cervical to the fourth dorsal. They report their researches on cardiac sensibility and the possibility of anchoring angina by resection of the posterior fibers of the spinal nerves, beginning the article by the statement that "we know positively that the radiation of the anginal pain is due to irritation of the centripetal paths, which contain both the sensory cardiac fibers and those to the cutaneous areas corresponding." They then raised the question of whether the painful syndrome in angina is visceral and cutaneous, or only cutaneous, as claimed by Mackenzie, thus marking the referred pains in the arm and neck as reflex in the cerebrospinal fibers of the medullary segments corresponding to the area of the heart or vessels affected. Other authors are of the opinion that the pain is provoked by a visceral disease, and is felt at the same time in the viscera and in the corresponding cutaneous area. The researches of Danielopolu and Hristide favor the hypothesis of Mackenzie that the pain is transmitted, that other sensations, palpitation, etc., are felt directly in the viscera.

Their observations were made on a syphilitic patient, aged 41, with aortic insufficiency and angina, which began July, 1918, following an emotional disturbance, when he had hard pain for a few moments. Attacks occurred rarely at first but later more frequently. Eight months after the first attack, one occurred at night, and following this, from ten to twenty a day occurred following the least effort or emotion. The pain was controlled with nitrite of amyl. Any food would produce it and the attacks came many times at night. The pain was retrosternal, and occurred also in the anterior surface of the left half of the thorax, radiating down the arm to the elbow. The arm pains were relieved somewhat by friction on the skin of the arm provoking strong irritation. The heart rhythm was regular, the rate from 74 to 94. There was some dilation of the right heart. The Wassermann test was positive. There was nothing special in the urine.

Anesthesia of the left dorsal spinal nerves in the intercostal tract and of the ramificantes was done with 8 cg of procain. The second and third dorsal branches were anesthetized, because minute study led them to localize

13 Danielopolu, D., and Hristide. Bull. et mem. Soc. med. d. hop. de Par. 47 69 (Jan 25) 1923.

the pain in the cutaneous areas supplied by these branches. Half an hour after, the patient was put through numerous tests, with a ten minute rest between, and although the heart rate mounted from 84 to 140 and the patient suffered from great shortness of breath and palpitation, there was no pain. The same efforts were repeated at the end of six hours when the effect of the procain had partly passed off. Characteristic pain followed, but nothing so severe as before the anesthesia, and after twenty-four hours, the least effort provoked a violent attack of pain. The authors drew the deductions as a result (1) that anginal pain is exclusively a transmitted pain, and is conveyed to the cutaneous areas of the same medullary segments that supply the heart and aorta, and (2) that all the sensory manifestations coming from the heart are not transmitted. In spite of the anesthesia of the corresponding spinal nerves, the patient was conscious of palpitations. If we except the anguish which appears to be due in part to the contraction of the pectoral and intercostal muscles, the other sensory manifestations of the heart, such as palpitation, sensations of extra systoles and those provoked by the onset of an attack of paroxysmal tachycardia, all have their origin in the affected viscera.

The authors claim for their method that they rob anginal attacks of the pain by suppressing the sensibility of the spinal nerves. These authors draw the further deduction that the Jonnesco operation, proposed by François Franck, of extirpation of the cervical-thoracic sympathetic system and successfully carried out twice by Jonnesco, the second time bilaterally, is inadmissible because it takes away from the heart nearly all of the extracardiac motor fibers except the sympathetic fibers of the vagus, and lessens the muscular function of the heart already diseased by angina. They claim further that this constitutes a predisposition to a systole of the left heart, contributing to pulmonary edema, a grave complication, which they state is frequently met with in angina with hypertension, and still further that this extirpation of the vasomotor fibers of the sympathetic system of the coronary arteries, which are probably vasodilators, diminishes coronary flow already jeopardized in angina. They claim that the resection of the posterior roots of the eighth cervical, first, second, third and fourth dorsal nerves, is a much less serious operation and does not touch the motor nerves of the heart. They admit the criticism that their operation does not suppress all of the centripetal paths in the cervical sympathetic cord, and state that if it is necessary they can be cut, but not resected. Finally they claim that the Jonnesco operation does not completely suppress all the cardio-aortic sensory tracts because the vagus is left intact.

In one case which they report, which came to operation, they cut only the second dorsal nerve, because the patient had a violent anginal attack during the operation.

Further communications are promised after prolonged observation of interesting phenomena, following their incomplete operation.

There seemed too much uncertainty about this operation and it is anything but simple. Besides, as Ranson points out, all the spinal connections would have to be cut very certainly, and possibly on both sides to insure freedom from pain.

From November, 1923, to the time this paper was written, the patient had spent most of the time in the hospital, under observation. For nearly two months he was in bed. Two grains quinin and  $\frac{1}{30}$  strychnin had influence in preventing his heart from fibrillating. A curious thing was made very evident on numerous occasions, and that was that his anginal attacks were followed immediately by fibrillation.

In addition to symptoms already described, he had attacks of apparent pain in the apex, which he felt as a drawing pain under the angle of the scapula on that same side. Occasionally these attacks were so severe that it took three doses of  $\frac{1}{100}$  gram of nitroglycerin to relieve them. On one occasion the attack lasted one-half hour without any relief. In the two months in bed before the second operation in March, 1924, he had twelve attacks.

The second operation was done under local anesthesia, and the superior ganglion was removed, and from that time to April 26, he had no attacks what-

ever although he was up and about all the time and took a moderate amount of exercise. Since the operation, however, he had a cough and some difficulty in swallowing. He did not swallow at all for twenty-four hours after the operation, and for a week thereafter he had a little trouble with swallowing liquids. He had tenderness in the back part of the left shoulder which disappeared in a few days. There was a slight pain in the angle of the left jaw when he began to eat at meals. Fibrillation occurred on several occasions since the operation, once lasting for three hours, but without pain. After the second operation, there was a roaring in the left ear and apparent deafness. The Rennie test was positive in the left ear. Bone conduction was normal. There was no disturbance of equilibrium. The throat specialist stated that the pain he complained of in the larynx after the removal of the stitches in the neck, was associated with a vesicular eruption on the larynx looking like herpes. This did not come for ten days after the operation.

**CASE 10** (Personal communication from Dr. Howard Naffsinger)—P. L., a man, aged 63, whose occupation was gardener and farmer. The diagnosis on entrance was angina pectoris and diabetes.

*Past History*—Patient lived in France from birth until aged 7 years, New York and vicinity from age of 27 to 45, California from age of 45 to 63. He had measles at 24, a mild attack with no sequelae. He had a mild attack of influenza at 30. He denies venereal history.

*Present Illness*—Twenty years ago the patient began having attacks of precordial pain. These came after exertion and especially followed exercise after meals. At first they would be from one to six months apart, but gradually became more frequent. For a period of six months they came on at the slightest exertion, so he had to stop work entirely for a period. The attacks lasted from three to fifteen minutes. He had to stop whatever he was doing. The pain was located just to the left of the lower part of the sternum, and he felt as though he were being torn apart. When the attack was severe, the patient did not fear death, but did feel a sense of impending death. In recent years, a feeling of numbness extended from the anterior part of the shoulder down the left arm to the wrist accompanying the attacks. Nitroglycerin, prescribed in the outpatient department, helped to cure the attacks. There were no symptoms of diabetes, but the urine was found to contain sugar, 2 plus. The blood chemistry sugar was 165. The patient was put on a diet, and the blood and urine became negative for sugar.

*Examination*—Irregular pulse. There was deep tenderness on the left side of the neck and shoulder. The chest was emphysematous and barrel shaped. There was an area of tenderness to percussion in the fourth left interspace just within the nipple line. The lungs were essentially normal except for hypostatic râles at both apexes. The heart was of normal size, and the sounds were of good quality. The second auricular was greater than the second pulmonary. A soft systolic murmur was heard at the apex only. Blood pressure varied from 205 systolic, 88 diastolic, to 160 systolic, 60 diastolic. There were palpable epitrochleas in both arms. The reflexes were all normal.

*Laboratory Examination*—Electrocardiogram showed the left axis deviation of plus 20, inverted T2 and T3. Auriculoventricular interval was at four twenty-fifths of a second. The urine and the blood were both normal. The Wassermann test was negative.

*Course in Hospital*—The patient had attacks of pain after walking from one to three times the length of the ward. On January 11, under local anesthesia, Dr. Naffsinger removed the superior cervical ganglion on the left. At one time during the operation the patient felt pain under the left clavicle similar to the pain he had been having, but not so severe.

*Postoperative Course*—The day after operation, the blood pressure varied from 124 systolic, 90 diastolic to 164 systolic, 60 diastolic. There was endophthalmitis with a small pupil that reacted to light on the left. There was no

hyperesthesia or pain. The patient was able to walk the length of the ward twenty times without pain. He continued to be in good condition and unaffected by exercise. However, on the third day postoperatively, the patient developed a dull epigastric and substernal pain, not definitely related to exercise, not so severe as the previous pain and with no sensation of tearing or pulling.

January 17, the patient was discharged. His condition was much improved. The heart findings were similar to those on entry except that there was no systolic murmur and the blood pressure was 175 systolic, 80 diastolic.

The diagnosis was generalized arteriosclerosis with chronic interstitial myocarditis and angina pectoris.

On January 25, the following note was made in the outpatient record. The day after operation the patient was able to walk a considerable distance without pain. He could then walk about ten blocks at an ordinary gait without symptoms. He might then get a gripping sensation referred to the heart region, which is different from the former heart pain. There was no dyspnea. The blood pressure was 200 systolic, 98 diastolic.

February 8, the patient had been at work since the last visit, tending chickens, pruning vines, etc. He did not work all day, but as much as he could. He had been feeling well until the last three days, since then he noticed some pounding of the heart and described a somewhat painful sensation over it. His pulse in the morning showed several extra systoles a minute, and from his description it was evidently the occurrence of these that he felt. Blood pressure was 196 systolic, 100 diastolic, with the first beat after the extra systoles were over 200.

#### REVIEW OF CASES REPORTED BY OTHERS, AFTER LEFT CERVICAL SYMPATHECTOMY

CASE 11—Dr M. A. Mortensen, of Battle Creek Sanatorium, Michigan, wrote us of a patient on whom he performed a left cervical sympathectomy. Unfortunately about two weeks afterward the patient died, but not of angina. The fact that the patient was a morphin fiend is set down as contributing to the death.

"It is, however, an interesting point to me that after the sympathectomy he did not have the typical angina pains. He had pains in the left shoulder which extended as low as the clavicle and which were due to the surgical trauma. Relief of the pain by the use of nitroglycerin failed entirely, and the patient stated that this was not the same pain he had formerly had. Furthermore, he stopped taking nitroglycerin after the second day, while before the operation he was taking it from thirty to forty times in the twenty-four hours, in doses of one-fiftieth to one-hundredth grain."

CASE 12—Dr Alexander Lambert, the correspondent, gave the following facts in regard to a patient operated on by Adrian Lambert in the fall of 1923. The patient was a woman, age not stated.

"An extremely poor subject for surgery, because she was so nervous, overwrought and physically exhausted and very nearly at the end of her rope, after two years of practically a *status anginosus*.

"The left superior ganglion was removed.

"She had a stormy month's convalescence, in which the irritation of the spinal accessory caused a terribly painful spasm in the trapezius muscles. Also taking out the superior sympathetic ganglion made a very painful set of reflexes along the ear and side of the neck."

The final result, however, "was to relieve entirely the pain on exertion and to enable the patient to go upstairs comfortably like an ordinary person, which she had not done for two years, to be able to sleep on either side, a new experience for her, and the cessation of intense pounding in her heart and rapidity of action on slight exertion."

Dr H. M. Marvin of the Yale Medical School, in a personal communication, reports the following two cases with a very definite contribution to the blood pressure studies during operation. His two patients were operated on by Dr S. C. Harvey.

CASE 13—The patient was a married Englishwoman, aged 54, who had been the subject of a few attacks of angina, classical in character, location and radiation, several years previously. They were followed by a period of freedom from pain, which was abruptly terminated by a seizure interpreted by us as due to coronary closure, intense substernal pain lasting for three days, relieved only partially by large doses of morphin and followed by intense weakness and dyspnea. Within the ensuing five weeks, even at rest in bed, she had four severe anginal attacks, shortly after the fourth, she came to the hospital.

Her past history was negative, except for typhoid fever and pneumonia in early adult life. She had scarlet fever in childhood, and frequent sore throats until a few years ago.

*Family History*—The patient's first husband died of pulmonary tuberculosis. By him she had one miscarriage at six months, followed by a normal child who still lives. She had no children by her second husband. Of three sisters, two are said to have died of heart trouble.

*Physical Examination*—Entirely negative except for evidences of heart failure, extreme dyspnea, orthopnea and weakness. The heart was not enlarged, the rhythm was regular, the sounds somewhat faint and no murmurs. The lungs were clear. The abdomen was normal. There was no edema of the extremities. Electrocardiogram was normal. Six-foot plate of the heart showed normal outline and no enlargement. Urine, blood and stools showed no abnormalities. Vital capacity was 42 per cent of normal.

The operation of the left cervical sympathectomy was performed by Dr Harvey, who evulsed the superior ganglion. The operation was on April 18 and since April 22 the patient suffered severely with pain and extreme hyperesthesia over the left side of the face, scalp, neck, shoulder, mammary and scapular areas, and frequently extending down the arm and forearm into the hand. Her symptoms resembled closely those attributed by Sluder to disturbance of the sphenopalatine ganglion. In the six months since the pain disappeared, it has been constant with the exception of three days, when it completely disappeared, only to recur as before at the end of that time.

It is interesting to note also that, although the operation relieved her completely of the precordial pain, it did not apparently stop the attacks. Four times since the operation, she has had attacks characterized by profound weakness, generalized sweating, fear of impending death, and a "queer, all-gone feeling" in the chest, symptoms which previously accompanied the anginal seizures, but there has been no actual pain with these later ones.

Our impression was that the patient had coronary closure six weeks prior to admission, in addition to typical angina. Operation was performed on April 18, 1923. The anesthesia was 0.5 per cent solution of procain. The cervical sympathetic was severed (left side), and the superior ganglion extirpated.

During the year that elapsed, the patient was in almost constant misery. With the exception of a few days when in the hospital, she had increasing pain involving the left half of face, scalp, neck, shoulder, left breast, and part of left upper arm. Within the last few months, signs of congestive heart failure (cyanosis, edema, etc.) have begun to appear. She has been many times under observation, the typical angina seizures, similar in all respects to those before operation, have been noted. There were typical eye and pupillary changes following the operation.

CASE 14—A man, aged 48, an Italian, had syphilitic aortitis, aorta insufficiency, and anginal attacks provoked by any moderate exertion or excitement. He had been having attacks for four years, which were growing worse within the last six months. The symptoms were always aggravated by antisiphilitic therapy. There were no signs or symptoms of congestive heart failure, the heart was not enlarged to physical examination or as shown in a six-foot roentgen-ray plate.

The operation was similar to that in Case 13, but with the addition of some gas-oxygen several times during the procedure, as the local anesthesia was not

entirely effective in abolishing pain. The left cervical sympathetic fibers were resected, with evulsion of the superior ganglion. Pain in the left side of the face and neck appeared on the fourth day, but disappeared within about ten days. The course of the patient was followed for eight weeks, during which time he had no recurrence of the chest pain, and found that he could do whatever he wished in the way of exertion. He considered himself cured, and returned to Italy, whence we have been unable to trace him.

The blood pressure did not show any significant change either during or after the operation. I took the pressures every two minutes throughout the operation, and three times a day for a week afterward. In both cases, it was a little higher at the conclusion of the procedure than at the beginning, but not as much as 10 mm.

Electrodiagrams were also taken throughout the operation at intervals of several minutes, and at the moment of cutting the nerves and evulsing the ganglions. The T waves were upright in all leads of both patients, and no changes of any sort were found. Tracings taken several weeks later remained unchanged.

CASE 15—Holmes<sup>14</sup> reported before the Chicago Society of Internal Medicine, Feb 25, 1924, a case of angina successfully operated on by Dr Wm Shackleton.

The patient was a woman, aged 53, white, who was admitted to Wesley Memorial Hospital on Jan 29, 1923, for treatment of cardiac failure. For about one year prior to the appearance of edema, dyspnea, and other signs of decompensation, she had vague pains in the precordium and left arm. During the first part of her hospital residence she did not complain of pain. The first attack of typical angina followed the effort of getting into a wheel chair. Thereafter, pain recurred with increasing frequency and severity until the slightest exertion was sufficient to bring it on. Nitroglycerin and amyl nitrite gave almost immediate relief but the subsequent prostration was extreme. On July 12, 1923, the superior cervical sympathetic ganglion was removed by Dr Wm E Shackleton and saved for histologic study. The patient was discharged from the hospital Aug 6, 1923, and soon thereafter was earning her living as a nurse in charge of two small children. At no time following the operation did she experience pain either in the thorax or in the left arm. Just a few days before the Christmas holidays she started on an automobile trip to Atlanta, Ga. En route she became ill and was admitted to the Nashville General Hospital. A letter from the hospital, dated Dec 29, 1923, stated that she complained of severe abdominal pain, nausea, vomiting and of precordial pain just before her admission. The temperature, pulse, respiration, blood pressure, etc., were reported to be about normal. She recovered from this undiagnosed illness, and we understand she was discharged from the hospital, but her subsequent history is unknown. During the six and one-half months she remained under our observation, she did not have a single recurrence either of thoracic or brachial pain.

Holmes had the advantage of the stimulating and helpful interest of Ranson,<sup>15</sup> to whom we owe a grateful acknowledgment of his similar help to us. Ranson made it clear to us that no sensory fibers from the heart were to be found above the middle cervical ganglion, and the relaying of pain could only be stopped by the removal of the lower cervical and first thoracic ganglions. The studies of Holmes and Ranson are valuable contributions to the understanding of angina but we are at a loss to explain the burning sensation in the base of the brain of one case, when the superior cervical ganglion was stimulated by a weak galvanic current during operation, and after the superior cardiac nerve and the main trunk had been severed. Holmes quotes Langley as finding no evidence of

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14 W H Holmes of the Department of Medicine, Northwestern University, Chicago

15 S W Ranson of the Department of Anatomy of the Northwestern University, Chicago

sensory pathways in the cervical sympathetic trunk by trial of electrical stimulation. With this point still not clear, we are left with the fact that the main recognized pathways of referred pain in angina were not touched, and yet the attacks are stopped by an operation which cuts two nerves, the superior cardiac and the main trunk between the superior and middle ganglions.

Bacon<sup>16</sup> reported a particularly severe case.

CASE 16—G J, a man, aged 78, was a moderate drinker and a very hard worker. Three years ago, while climbing a hill, he was suddenly seized with a heavy feeling in the chest, over the precordium, which quickly disappeared on resting. Since then, similar attacks have followed exertion, with increasing frequency, and in March, 1923, they began to awaken him from sleep and became more frequent and severe at night. By April, severe attacks followed any excitement or exertion, such as coughing, eating or defecation, besides these, apparently spontaneous ones became very frequent. Rest and medical treatment gave only brief relief. His appetite disappeared, and vomiting frequently followed an attack. With increasing frequency and severity of attacks,  $\frac{1}{400}$  grain tablets of nitroglycerin were given under the tongue every half hour as a preventive, but without success. Slight temporary improvement followed the use of spirit of glyceryl trinitrate. June 13, after weeks in bed, the patient was receiving the equivalent of  $\frac{1}{400}$  grain of nitroglycerin under his tongue, by a trained nurse, every fifteen minutes night and day, whether sleeping or waking, from fifteen to twenty-five pearls of amyl nitrite during the twenty-four hours, 2 grains of sodium nitrite and  $\frac{1}{4}$  grain of morphin every three hours. In spite of this heroic dosage, he suffered eight severe attacks in six hours, during which the family thought the patient was dying and had the last sacraments of the church administered.

June 14, after the patient had passed a night of terrific suffering, under 1 per cent procain local anesthesia, the left superior cervical ganglion was removed in toto.

August 14, two months after the operation, the patient was very cheerful and contented. His appetite was good and he slept well, he could also walk a mile a day without discomfort. He was not so short of breath as formerly. His greatest difficulty came during and after eating, when he had a feeling of pressure around the heart.

November 12, five months after operation, the patient reported that he was in better health than he had been during the last two years. He had gained 26 pounds (12 kg), and his waist measure had increased 4 inches (10 cm) in circumference. He frequently slept six hours at a stretch, and ate everything. Overeating, however, was followed by a feeling of fulness and pressure on the level of the sixth rib at its cartilage articulation on the right side. He had not experienced any pain in the heart region, but had an aching pain in both arms and hands when they were cold or he was cold, and when he became excited.

#### SUMMARY

Cutting the left superior cardiac branch of the cervical sympathetic and the main trunk below the ganglion has relieved the main condition in anginal attacks, and apparently the one from which the patients die in attacks. In a few cases, referred pains are not entirely relieved.

Jonnesco's original operation of removing all of the left cervical sympathetic tract and its three ganglions, and the first dorsal ganglion, has accomplished no more than this, for in Kappis'<sup>8</sup> case the character-

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16 Bacon, J H. Left Superior Cervical Sympathectomy Under Local Anesthesia in Angina Pectoris, J A M A 81 211 (Dec 22) 1923

istic attacks of angina recurred after four months Jonnesco called attention in his original article to the need of bilateral removal, and it is possible in our own cases with incomplete relief of all symptoms that a bilateral operation would have brought complete relief Jonnesco's patient declined the right sided operation because he was relieved without it With our all too slight knowledge of the pathways from brain and cord to heart and their complete function, it is not right to condemn the procedure because of its failure in a small number of cases, at least until the similar operation has been done on both sides

It seems clear to us that our operation removes the main cause of angina This is based on the supposition (1) that angina is due primarily to spasm of the aorta but it may be also of the coronaries, for they are supplied by the same nerve systems of the sympathetic The spasm is most commonly in the aorta but it may occur alone in the coronaries, (2) that the superior cardiac nerve has a constrictor action, and cutting it prevents the spasm Our right sided case shows that it is possible that the bilateral operation is necessary in some cases, for in that case an unusually severe attack produced pain also in the left side of the neck and left arm, and frequently in cases with mainly left sided radiations an unusually severe attack will cause right sided radiations, (3) Case 3, Series 1,<sup>2</sup> reported again as Case 9 in this series, after removal of the left superior ganglion one and one-half years after severing of the superior cardiac nerve and main trunk of the sympathetic below the ganglion, shows that heart pain distinguished from substernal pain which we are attributing to aorta spasm, is in some way influenced by this upper ganglion From twelve attacks during the three weeks in bed before the second operation he has had none in the four weeks since although up and about It may be through vagus connections, and herein lies what possibilities there are in the Wenckebach-Eppinger-Hofer theory, that there is a separate depressor nerve, which when cut relieves angina The superior laryngeal and the vagus which are said to give rise to this depressor nerve in man as they do in some animals, both have connecting branches to the superior ganglion

It would seem that our operation removes the cause of the anginal attack, and that the more elaborate operation of Jonnesco removes the cause and also removes other motor and sensory pathways

The operation may have to be bilateral to relieve completely all pain

Only in event of further investigation can the limits be defined In the meantime sixteen more cases of relief by removal of the superior ganglion are herewith reported, including our own, with two deaths, and fourteen with relief of the main symptoms



# THE REACTION OF THE LIVER TO PHENOL- TETRACHLOROPHTHALEIN IN EARLY OBSTRUCTIVE JAUNDICE \*

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Attempts to measure the functional powers of the liver by various tests have occupied a rather prominent position in recent medical literature. The phenoltetrachlorophthalein test during the last few years has given promise of being the most valuable of the various methods proposed. Abel and Rowntree,<sup>1</sup> in 1909, discovered that, except for traces which appeared in the urine, this dye was apparently eliminated only by the liver after subcutaneous or intravenous injection of the disodium salt. They also found that the substance was nontoxic to dogs, even when injected daily for several months in very large doses. They noticed, moreover, that subcutaneous injections of the dye had a prolonged laxative action. Several years later Rowntree, Hurwitz and Bloomfield,<sup>2</sup> Whipple, Mason and Peightal,<sup>3</sup> and Whipple, Peightal and Clark<sup>4</sup> undertook clinical and experimental investigations on the elimination of this dye by the liver and its applicability as a clinical test for liver function. Their method consisted in the intravenous injection of the disodium salt, and subsequent collection of the feces for the next forty-eight hours which were examined for their dye content. They found that approximately from 50 to 60 per cent of the unchanged dye was excreted by the liver, and in agreement with the work of Abel and Rowntree that the first portion of the dye to be excreted was in a conjugated form. They also observed that a trace of the dye, especially when large doses were given, appeared in the urine in a conjugated and also in a free form. They felt, however, that the test was not easily applicable because of uncertainties in the collection of the feces, and also because in cases in which there was obstruction

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\* From the Snyder Fund and the Otto Baer Fund for Clinical Research of the Michael Reese Hospital and the Nelson Morris Memorial Institute for Medical Research

1 Abel, J J, and Rowntree, L G J Pharmacol & Exper Therap 1 231, 1909

2 Rowntree, L G, Hurwitz, H, and Bloomfield, A L Bull Johns Hopkins Hosp 24 327, 1913

3 Whipple, G H, Mason, V R, and Peightal, T C Bull Johns Hopkins Hosp 24 207, 1913

4 Whipple, G H, Peightal, T C, and Clark, A H Bull Johns Hopkins Hosp 24 343, 1913

to the outflow of bile the dye could not be recovered from the feces McNeil<sup>5</sup> modified the test by recovering the duodenal contents by means of the Einhorn tube after injection of the dye. He concluded from his studies that the amount of dye eliminated was of little value, but that its appearance time was delayed in certain pathologic changes in the liver. Kahn<sup>6</sup> utilized the Lyon-Meltzer method of securing a flow of bile after intravenous injection of the dye. In 1922, Rosenthal<sup>7</sup> still further modified the test. His procedure was to inject the dye intravenously in a dosage of 5 mg of the disodium salt per kilogram of body weight, and then to examine specimens of blood serum taken at various intervals after the injection for their dye content. He observed that in normal animals the dye almost entirely or entirely disappeared from the blood stream within one hour. On removal of parts of the liver or on injuring that organ by poisons, such as chloroform, he found that various amounts of the dye were retained in the blood stream for more than one hour after injection. He extended his observations to human beings, and reported that in many diseased conditions in the liver there was a retention of the dye in the blood stream. Moreover, he found no retention of the dye in the blood stream of dogs when injected shortly after ligation of the common duct. Ottenberg and Rosen<sup>8</sup> found complete retention of the dye in three of four patients who had complete biliary obstruction of long duration.

The experiments reported in this paper were undertaken with the view to determine the fate of phenoltetrachlorophthalein after intravenous injection, immediately after ligation of the common and cystic ducts and to correlate these findings with the results of the Van den Bergh<sup>9</sup> test. The cystic duct was to be tied to prevent excretion of the dye into the gallbladder by the liver.

We found it necessary to modify slightly Rosenthal's<sup>10</sup> technic. He injected 5 mg of the disodium salt per kilogram of body weight and then took samples of the blood serum fifteen and sixty minutes after injection of the dye, and on the addition of 3 drops of 5 per cent sodium hydroxid to 1 c c of the dye containing serum he was able to

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5 McNeil, H. L. *J. Lab. & Clin. Med.* **1** 822, 1915.

6 Kahn, Max. Phenoltetrachlorophthalein Estimation in the Duodenal Contents, *J. A. M. A.* **77** 41 (July 22) 1921.

7 Rosenthal, S. M. *J. Pharmacol. & Exper. Therap.* **19** 385 (June) 1922, A New Method of Testing Liver Function with Phenoltetrachlorophthalein, *J. A. M. A.* **79** 2151 (Dec. 23) 1922, *Bull. Johns Hopkins Hosp.* **33** 432 (Dec.) 1922.

8 Ottenberg, Reuben, and Rosen, Samuel. Possible Application of Phenoltetrachlorophthalein Test to Obstructing Jaundice, *J. A. M. A.* **80** 1519 (May 26) 1923.

9 Van den Bergh, A. A. H. *Presse med.* **29** 441 (June 4) 1921.

10 Rosenthal, S. M. *Proc. Soc. Exper. Biol. & Med.* **21** 73 1923.

read his test specimen against standard solutions of the dye of various strengths. We found this method very difficult, and capable of giving quite variable readings with various portions of the same specimen because of hemolysis, bilirubinemia or lipemia. We observed that the addition of one volume of acetone to one of the test serum precipitates the proteins sufficiently to leave on centrifugalization a water-clear supernatant fluid. The addition of 3 drops of 5 per cent sodium hydroxid to this fluid shows the minutest traces of the dye, amounts of the dye which were usually not demonstrable by the Rosenthal method in our hands. The white precipitate does not change color on the addition of 5 per cent sodium hydroxid. This method is, moreover, much more accurate with respect to the actual colorimetric readings in all concentrations of the dye because of the absence of opalescence in the test specimen. A permanent standard for reading the values of the dye in acetone treated serum was made up according to the Rosenthal<sup>10</sup> method, using distilled water alone as the diluent, except that, for each reading, the standard solution was made twice as strong and then diluted with an equal volume of acetone so as to give a color comparable to that of the test serum. After a month the acetone standard began to fade slightly.

It is to be noted that there is some confusion in the literature with respect to the use of the words plasma and serum. In some reports,<sup>7</sup> the term plasma is used when the protocols show clearly that serum and not plasma was actually meant.

In all of our experiments a preparation of the disodium salt of phenoltetrachlorphthalein was injected in an equal volume of physiologic sodium chlorid solution.

## RESULTS

As a control experiment it was thought advisable to remove the liver entirely from the circulation in dogs, to inject phenoltetrachlorphthalein intravenously and to observe the blood stream for its content of the dye at various periods. The results of these experiments are tabulated in Table 1. A typical protocol (Dog 4, Table 1) is given of these experiments. It was thought advisable, moreover, to remove the kidneys, as it has been shown that when an excessive amount of the dye was injected the kidneys excreted a portion of the excess.

## PROTOCOLS OF EXPERIMENTS

EXPER 1—Dog 4 (Table 1), female, mongrel, weight, 17 kg, under anesthesia of 1 grain of morphin, the right carotid artery was cannulated and a specimen of blood removed. The abdomen was incised in the midline. Ether anesthesia was then begun. The portal vein and hepatic artery were tied off, the liver was dissected from the inferior vena cava and the hepatic vein, these

vessels were ligated and the liver extirpated. Ether was discontinued. One hundred milligrams of the dye was injected intravenously. Specimens of blood taken from the carotid artery at the end of fifteen minutes, and from the left side of the heart at the end of one hour contained more dye than could be read on the colorimeter.

From Table 1 it may be seen that after intravenous injection of phenoltetrachlorophthalein after previous extirpation of the liver and kidneys the dye was apparently completely retained in the blood stream.

A series of experiments on five dogs was then performed in which

TABLE 1—*Injection of Phenoltetrachlorophthalein After Extirpation of the Liver and the Kidneys*

Dog	Weight in Kg	Mg of Dye Injected	Time in Minutes Dog Lived after Injection of Dye with Liver and Kidneys Out	Amount of Dye in Blood of Left Heart at End of Experiment
1	18	250	32	40%*
2	10	100	22	40%
3	22	250	38	40%
4	12	100	67	40%
5	17	200	16	40%

\* More than 40 per cent of dye cannot be demonstrated in the blood serum by any technic now in use, irrespective of the amount of dye injected.

TABLE 2—*Injection of Phenoltetrachlorophthalein After Removal of Kidneys and Ligation of the Common and Cystic Ducts*

Dog	Weight in Kg	Mg of Dye Injected	Amount of Dye in Blood after 1 Hour	Van den Bergh of Blood at End of 1 Hour	Dye in Hepatic Duct at End of Experiment	Dye in Gallbladder at End of Experiment	Remarks
1	17	150	0		++++	++++	Cystic duct not ligated
2	16	250	0	Indirect in 15 minutes, direct in 60 minutes	0	0	
3	15	150	0	Faint indirect?	0	0	
4	17	250	7%	Very strong indirect	2%	0	Four times normal dose
5	8	120	5%	Direct +++++	Trace	0	Ten days after ligating the common duct

the kidneys were removed and the common and cystic ducts ligated. Into these animals the dye was injected intravenously, in dosages varying from 5 to 10 mg per kilogram of body weight. In these experiments the blood was examined by the Van den Bergh test, and for its dye content. At the end of the experiment the bile of the hepatic duct and the various organs and tissues of the body were tested for the presence of the dye (Table 2). A typical protocol of the five experiments is appended (Dog 2, Table 2).

EXPER 2—Dog 2 (Table 2), yellow, male mastiff, weight 16 kg, was anesthetized with ether and 1 grain of morphin. The kidneys were removed and the common and cystic ducts ligated. Two hundred and fifty milligrams of

the disodium salt of phenoltetrachlorophthalein was injected into the right jugular vein. The blood at the beginning of the experiment gave a negative Van den Bergh reaction. Fifteen minutes after injection there was a faint indirect Van den Bergh reaction in the blood, and at the end of one hour there was a positive direct Van den Bergh reaction. At the end of fifteen minutes there was practically none of the dye in the circulation. At the end of one-half hour no dye whatever was demonstrable. The animal was allowed to live two hours after injection of the dye. It was found at necropsy that the lymphatics at the hilum of the liver were of a distinct yellow color. The thoracic duct was enlarged and quite golden yellow. The bile from the proximal portion of the hepatic duct contained none of the dye. The cut section of the liver did not change color on application of 5 per cent sodium hydroxid. Portions of the liver, heart and lungs were boiled with 5 per cent sodium hydroxid and 5 per cent hydrochloric acid and none of the dye was demonstrated.

To test the possibility of the dye having broken down in the liver, with a resultant liberation of chlorin, a portion of the liver was examined quantitatively for its free chlorids by the urine chlorid method of Vollhard and Harvey,<sup>11</sup> after incubation at 37.5 C (for twenty-four hours) in distilled water in the presence of thymol dissolved in ethyl alcohol. This was not found to be higher than that of an equal portion of normal dog liver. Because of the small amount of chlorids present and the resulting high percentage of error, it is felt that no conclusions are justified from these chlorid determinations.

The results of these experiments were considered exceedingly interesting, since one of us<sup>12</sup> had shown that in similar experiments, without the injection of the dye, an indirect reaction by the Van den Bergh method was seldom obtained before two hours after tying the biliary ducts. He also found that the indirect Van den Bergh reaction alone was obtained during the first day after ligation of the common and cystic ducts and after this the direct reaction appeared.

After this, similar experiments were then performed on five dogs in which the thoracic duct was also cannulated and the lymph tested by the Van den Bergh method and for its dye content. These experiments, which are presented briefly in Table 3, indicate that with the exception of the experiment on Dog 5, practically none of the dye appeared in the lymph stream. In this animal, twenty-two days elapsed between the ligation and section of the common duct and the injection of the dye. The animal was severely jaundiced, and after the introduction of the dye it was found that the lymph very soon showed the presence of the dye in a concentration almost equal to that in the blood stream. Because of this experiment, it was felt that in chronic obstructive jaundice, where there is microscopic evidence of severe damage to the liver cells, the liver, being unable to remove all of the dye brought to it by the blood stream, turns over part of it into the lymph channels. We believe, however, that there is no parallelism between

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11 Harvey, S. C. The Quantitative Determination of the Chlorids in the Urine, *Arch Int Med* 6:12 (July) 1910.

12 Bloom, W. *Bull Johns Hopkins Hosp* 34:316 (Sept.) 1923.

the reaction of the liver in early obstructive jaundice to bilirubin and to phenoltetrachlorophthalein. For, in acute experiments, the former is present in increasingly greater amounts in the thoracic duct, while the latter hardly appears at all, even when very large doses are injected intravenously.

The liver tissue of five animals in the preceding experiments, in which the injected dye disappeared from the blood stream, was subjected to the action of boiling 5 per cent sodium hydroxid and 5 per cent hydrochloric acid, and of reducing and oxidizing agents, such as dilute iodine, potassium permanganate, hydrogen peroxid and nascent hydrogen. It was impossible to recover dye after any of these procedures. Nor was it possible on repeated trials to demonstrate a higher chlorid content in these than in normal livers.

In another series of experiments, 5 gm each of the following organs from four normal dogs were minced and suspended in 4 c c of physio-

TABLE 3—*Injection of Phenoltetrachlorophthalein After Ligation of Common and Cystic Ducts and Cannulation of Thoracic Duct and Removal of Kidneys*

Dog	Weight in Kg	Mg of Dye Injected	Time Lapse Between Ligating Common Duct and Injection of Dye	Phenoltetraehlorphthalein in Blood		Phenol-tetraehlorphthalein in Lymph
				End of 30 Minutes	End of 60 Minutes	
1	10	70	0	0	0	0
2	5	40	2 hours	+	0	Trace
3	40	250	2 hours	3%	0	0
4	5	50	5 hours	+	0	0
5	10	100	22 days	5%	4	3%

logic saline solution. To each specimen one drop of 0.5 per cent of disodium phenoltetrachlorophthalein and two drops of thymol solution in ethyl alcohol were added and incubated at 37.5 C (99.1 F). The specimens were examined for the presence of the dye after one, two, six and eighteen hours. The organs tested were the striped muscle, heart, lung, kidney, liver, spleen, and large bowel. It was found that at the end of twenty-four hours the heart had so changed the dye that practically none of it could be demonstrated after hydrolysis with 5 per cent sodium hydroxid and 5 per cent hydrochloric acid. The lung and spleen also decolorized the dye more than the liver. The striped muscle seemed to have no effect on the dye.

#### SUMMARY OF EXPERIMENTAL RESULTS

The experiments reported in the foregoing showed that in the absence of the liver and kidneys the dye remained in the circulation as long as the animals lived. After tying the common and cystic ducts, the liver was able to remove large quantities of phenoltetrachlorophthalein.

from the circulation The dye in these experiments was not excreted in significant quantities by the liver into the bile passages, and it did not appear in the lymph of the thoracic duct We were unable to recover the dye from these livers by treating them with hydrochloric acid, sodium hydroxid, oxidizing or reducing substances, so that we believe that the liver cells either combined very intimately with the dye or else changed it into a more or less stable, colorless compound or compounds It was thought that if the phenoltetrachlorphthalein was broken down in the liver, some of its chlorine might be liberated We have no evidence to support this theoretical liberation of chlorine We

TABLE 4—Series of Patients Suffering from Various Diseases

Cases	Number of Cases	Number Showing Increase in Indirect Van den Bergh Reaction		Average Amount of Dye in Urine	Untoward Reactions			Total Number of Cases Showing Untoward Reaction
		Number or in Direct when Positive	Number Showing Abnormal Dye Retention at End of 1 Hour		Number Showing Thrombosis	Chills	Sterile Abscesses or Local Reaction	
Group 1 Miscellaneous without liver diseases	8	8	0	Less than 0.5 mg	2	1	—	2
Group 2 Miscellaneous with liver disease, carcinoma, amyloid, syphilis, tuberculosis	5	5	3 (3-7%)*	Less than 0.5 mg	1	—	1	2
Group 3 Cardiac decompensation (chronic passive congestion of liver)	4	4	4 (4-9%)	Less than 0.5 mg	1	—	1	2
Group 4 Acute and chronic cholecystitis with or without cholelithiasis	4	4	0	0.5 mg	—	1	2	2
Group 5 Laennec's atrophic cirrhosis of liver	3	3	3 (7-8%)	Less than 1 mg	—	—	1	1
Group 6 Obstructive jaundice								
Due to stone	2	1	1 (2%)	Less than 1 mg	—	—	1	1
Due to cholangitis	1	1	1 (4%)					
Total	27	26	12		4 (14.8%)	2 (7.4%)	6 (22.2%)	10 (37.0%)

Amount of dye injected routinely 5 mg per kilogram of body weight  
\* The percentage figures in this column indicate the amount of dye retention

have been unable to determine the fate of the dye in the liver of the dog in early obstructive jaundice The finding that the intravenous injection of phenoltetrachlorphthalein causes a very rapid appearance of the indirect and direct Van den Bergh reactions is considered more fully when the results of our clinical studies are discussed

CLINICAL RESULTS

A series of patients suffering from various diseases, and a number of apparently normal persons were injected with 5 mg of the dye per kilogram of body weight and at the end of one hour the blood was

examined by the Van den Bergh test and for its dye content. We noticed that the fifteen minute specimen added nothing to the information obtained from the hour specimen of serum.

Here again, the findings first noticed in the experiments on the dogs in Table 2 were confirmed and extended. It was seen that even in normal persons there was a transient hyperbilirubinemia, as evidenced by a quantitative increase of the indirect Van den Bergh reaction. This hyperbilirubinemia, which usually disappeared within twenty-four hours, seemed to bear no relation to the severity of impairment of liver function as measured by the dye retention. We believe that the transient bilirubinemia subsequent to the injection of phenoltetrachlorophthalein was due to the fact that the liver, having an apparently specific, excretory action toward the dye after it had been injected intravenously, cannot excrete bilirubin or its precursors which are brought to it until all of the dye has been eliminated. We have no evidence that this transient bilirubinemia is indicative of anything more than a temporary functional blockade of the bilirubin excreting power of the liver. As a control experiment, phenoltetrachlorophthalein was added to blood serum *in vitro*, it had no apparent effect on the Van den Bergh test. The dye alone, moreover, did not give a color reaction with Ehrlich's diazoreagent.

As may be seen from Table 4, 14.8 per cent of the patients injected with the dye developed thromboses at the site of injection, 22.2 per cent local reactions, 7.4 per cent chills, a total of 37 per cent untoward reactions were met with in this series. Small traces of the dye in a free or a conjugated form were found in the urine of normal persons as well as patients suffering from various types of liver disease. The total amount of the dye in the urine was never more than 3 mg., that is, less than 1 per cent of the total dye injected. In none of our cases with complete biliary obstruction have we ever found a dye retention greater than 4 per cent. This is in agreement with our findings in experimental animals and at variance with the results of Ottenberg and Rosen.<sup>8</sup>

#### CONCLUSIONS

- 1 In the absence of the liver and kidneys, phenoltetrachlorophthalein continued to circulate in the blood stream.

- 2 The intravenous injection of phenoltetrachlorophthalein in the early stages of obstructive jaundice in dogs caused an earlier appearance of both the indirect and the direct Van den Bergh reactions that was noticed in control animals.

- 3 All attempts to recover the dye from the liver in obstructive jaundice were unsuccessful.

- 4 Dog liver decolorized phenoltetrachlorophthalein less than the heart, lung, and spleen *in vitro*.



5 In early obstructive jaundice, phenoltetrachlorophthalein appeared in minute amounts or not at all in the lymph of the thoracic duct. In chronic obstructive jaundice, however, the dye was present in large amounts in the lymph of the thoracic duct.

6 The intravenous injection of phenoltetrachlorophthalein produced in the human being a transient hyperbilirubinemia, as evidenced by the Van den Bergh test.

7 The high incidence of thromboses and other untoward reactions after the injection of phenoltetrachlorophthalein, is a serious objection to the execution of this test as a clinical method.

8 In no case of long standing complete biliary obstruction have we noticed a greater dye retention than 4 per cent in the blood serum.

9 A new method is given for the accurate determination of small amounts of phenoltetrachlorophthalein in blood serum.

# MITRAL STENOSIS WITHOUT RHEUMATIC FEVER IN NORTH CHINA \*

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Ever since the etiologic relationship between rheumatic fever and stenosis of the mitral valve was established half a century ago by Hayden,<sup>1</sup> Fagge,<sup>2</sup> and Duckworth,<sup>3</sup> these two conditions have been closely associated in the minds of European and American students of

TABLE 1—*Relative Incidence of Mitral Stenosis in Peking and Elsewhere*

Hospital	Years	Medical Patients	Cases of Mitral Stenosis	Per Cent Mitral Stenosis
St Bartholomew's, London	1913	1,996	50	2.5
Johns Hopkins, Baltimore	1914	1,422*	17	1.2
P U M C, Peking	July 1, 1921 to Jan 31, 1924	2,694	39	1.45

\* White patients only are included. Among 311 negro patients there were no cases of mitral stenosis.

TABLE 2—*Relative Incidence of Rheumatic Fever and Infection Arthritis in Peking and Elsewhere*

Hospital	Years	Medical Patients	Fever		Arthritis		Totals	
			No	%	No	%	No	%
St Bartholomew's, London	1913	1,996	105	5.26	1	0.05	106	5.3
Johns Hopkins, Baltimore	1914	1,422*						
P U M C, Peking	July 1, 1921 to Jan 31, 1924	2,694	6†	0.2	6	0.2	12	0.4

\* White patients only are included.

† These include cases of rheumatic fever.

‡ None of these was as severe as the typical cases of rheumatic fever seen in America.

heart disease. It is interesting to discover, therefore, that in North China, where typical rheumatic fever is almost unknown, mitral stenosis is the most common heart lesion, and its incidence is comparable to that in western countries. Table 1 shows the prevalence of mitral stenosis in our records as compared with those of St Bartholomew's Hospital, London, for 1913, and of the Johns Hopkins Hospital, Bal-

\* From the Department of Medicine, Peking Union Medical College.

1 Hayden: Diseases of the Heart and the Aorta, Dublin, 1875, p. 964 (quoted by Duckworth).

2 Fagge, C. H.: On the Murmurs Attendant upon Mitral Contraction, Guy's Hosp. Rep., 3rd Series, 16: 247, 1871.

3 Duckworth, D.: On the Aetiology of Mitral Stenosis, St Barth's Hosp. Rep. 13: 263, 1877.

timore, for 1914. In contrast to this, Table 2 shows the relative incidence of rheumatic fever and infectious arthritis in the same hospitals.

This paper deals with thirty-nine cases of mitral stenosis occurring in Chinese patients. These include all of the definitely diagnosed cases of this condition which have been admitted to our wards since the new hospital was opened. We have included only patients which presented the typical physical signs of the disease, namely, a presystolic thrill and a presystolic rumbling crescendo murmur (or its equivalent in the presence of auricular fibrillation) localized to the apical region of the heart. No cases of marked aortic insufficiency are included, in which the apical murmur could be mistaken for a so-called Austin Flint murmur.

#### RHEUMATIC ANTECEDENTS

We have reviewed these cases particularly from the standpoint of their etiologic relationship to rheumatic fever, acute arthritis and chorea, the three conditions which were termed by Duckworth "rheumatic antecedents." Of the thirty-five cases in which our records make a definite statement, only one gave a history of rheumatic fever, and one a history of chorea, while fourteen others gave a history of joint

TABLE 3—*Relative Incidence of Rheumatic Antecedents in Cases of Mitral Stenosis*

Cases Reported by	No. of Cases	Rheumatic Antecedents				Per Cent
		Rheumatic Fever	Chorea	Joint Pains	Total	
Duckworth	80	47	4	5	56	70.0
Meleney and Kellers	35*	1	1	14	16	45.7

\* In four cases there was no record whether or not there had been joint pains.

pains of varying intensity. The patient with a history of rheumatic fever stated that fifteen years ago, at the age of 12, she had had fever with painful, red and swollen joints. This had recurred five or six times since then. Of the fourteen patients listed as having had joint pains, five had had fever (two of them slight) and in all these multiple joints (four or more) had been involved. Ten patients in all had multiple joint pains, one had three joints involved, three had only two. Swelling of joints occurred in only one patient. Redness of joint regions never occurred. The patient with a history of chorea stated that he had had it at 12 years of age, five years before admission, and that it lasted for one year.

These cases present a strong contrast to those of Duckworth.<sup>3</sup> Of his eighty cases of mitral stenosis fifty-six patients had had rheumatic

antecedents Of these, forty-six had had one or more typical attacks of rheumatic fever Four had had chorea alone and one both chorea and rheumatic fever Three had had "rheumatic pains," one "rheumatic gout" and one osteoid arthritis Table 3 shows the contrast between these patients and ours

In the absence of more definite rheumatic antecedents in these cases we have searched for other etiologic factors, but no greater tendency to other known infections has appeared than is met with in the general taking of histories For instance, only ten of our patients gave a history of sore throats, and of these, only three had had joint pains as well Five patients had had toothache, and three of these had had joint pains also Four had had otitis media, and one of these joint pains also Thirteen had a history of smallpox, twelve of measles, five of typhoid or some similar type of fever, and four of gonorrhea, with joint pains in one of these

#### PHYSICAL EXAMINATION

The general physical examination revealed no more definite evidence of sources of infection than did the history In twelve patients the tonsils were enlarged, in eight of these they were cryptic, and in two inflamed as well In fifteen the teeth showed pyorrhea, in only five was there caries, and in three others, root abscesses Three patients were slightly deaf in one ear, one of these had a thickened and retracted ear drum One patient had tuberculosis of the lungs and of the humerus In one the history and physical signs pointed to a gonococcal salpingitis

In other features our series of cases corresponds closely to those reported elsewhere Although there are only fourteen female patients in our series as against twenty-five males, this inversion of the usual proportion in mitral stenosis is practically abolished when it is considered that our total number of male medical patients has outnumbered the females by 32 to 1 This correction brings the theoretical percentage to females 62.7 per cent, males 37.3 per cent This corresponds closely to the ratio in the cases collected by Duckworth females 67.3 per cent, males 32.6 per cent

#### AGE GROUPS

The age groups also correspond fairly closely to those reported by Duckworth, as shown in Table 4 The highest incidence in our series, however, is reached in the second decade, whereas in Duckworth's series, the third and fourth decades had the highest incidence and were nearly equal Table 4 also shows the age of onset of symptoms in our series It will be seen that the second decade has by far the largest incidence of onset, increasing over the simple age incidence at the

TABLE 4—*Age Distribution of Cases of Mitral Stenosis*

Age, Decade	Duckworth's Cases	P U M O Cases	P U M C Onset of Symptoms
1	0	1	1
2	14	12	18
3	24	9	8
4	23	8	4
5	13	6	5
6	5	3	3
7	1	0	0
Total cases	80	39	39

expense primarily of the fourth decade. The close correspondence of the "incidence" and "onset" columns in the fifth and sixth decades may be due either to a late onset of the pathologic process, or to a very mild lesion of long standing which first gave symptoms only when the myocardium began to grow old. This latter possibility is supported by the necropsy findings in Case 35, which are mentioned later.

#### ELECTROCARDIOGRAPH FINDINGS

In connection with the diagnosis of our cases of mitral stenosis it is interesting to note the abnormalities shown by the electrocardiograph. These were as follows:

Of thirty-five cases on whom records were taken, there was right ventricular preponderance in eighteen cases, auricular fibrillation in thirteen cases, auricular fibrillation constantly in six cases.

Of the twenty-nine cases in which the P wave was present, there was notching of the P wave in seventeen cases, flat top P wave in four cases, inverted P wave in Lead 3 in eight cases, P-R interval above 0.20 seconds in seven cases, deflection of P wave above 0.2 millivolts in fourteen cases.

It is noteworthy that, in two instances in our series, two cases were present in the same family. Cases 25 and 28 are brother and sister. Both have a history of vague joint pains. Again, Case 34 is the mother of Case 1. In neither case were any "rheumatic antecedents" known.

Out of thirty-seven patients in which a blood Wassermann test was performed, four were positive (4 plus). Three of these cases had no "rheumatic antecedents." The other patient had joint pains lasting for three months at the time of onset of heart symptoms four years ago. No opportunity has been offered to check up the diagnosis on these cases at necropsy.

One of our patients had paralysis of the left recurrent laryngeal nerve, a complication of mitral stenosis which has often been reported.<sup>4</sup>

<sup>4</sup> Garland, J., and White, P. D. Paralysis of the Left Recurrent Laryngeal Nerve Associated with Mitral Stenosis. *Arch Int Med* 26:343 (Sept.) 1920.

TABLE 5—Analysis of Thirty-Nine Cases of Mitral Stenosis in Peking

Case	Sex	Age	Age at Onset	Rheumatic Fever	Chorea	Joint Pains	Other Infections	Was-ser-mann	Right Ventricle Preponderance	Auricular Fibrillation	Electrocardiogram				P-R Intervals in Seconds	Deflection of P in Millivolts	Remarks
											Notched P	Flat Top P	Inverted P Lead 3	P-R			
1	M	10	10	0*	0	0	† 4, 8	0	+	0	+	0	+	0.14	0.25		
2	M	14	12	0	0	0	† 4, 8	0	+	0	+	0	+	0.18	0.8		
3	F	15	13	0	0	+	1, 5, 7	0	0	+	0	+	0	0.2	0.15	Died, no necropsy	
4	M	15	14	0	0	+	4, 2, 6?	0	—	—	—	—	—	0.24	0.25	Died, necropsy	
5	M	16	11	0	0	+	0	0	+	0	+	0	+	—	—		
6	M	17	14	0	0	+	0	0	+	0	+	0	+	0.18	0.25	Died at home	
7	M	17	17	0	0	0	4?	0	+	0	+	0	+	0.16	0.5		
8	M	17	11	0	0	0	1, 5, 9	0	+	0	+	0	+	0.16	0.1		
9	M	17	12	0	0	0	3, 9	0	+	0	+	0	+	0.24	0.15		
10	M	18	17	0	0	+	2	0	+	0	+	+	+	0.16	0.3	Paralysis left recurrent laryngeal nerve	
11	M	18	17	0	0	—	7, 8	0	+	0	+	+	+	0.16	0.3		
12	F	20	20	0	0	0	2	0	0	0	+	0	+	0.16	0.3		
13	M	20	18	0	0	0	3, 7	0	+	0	+	0	+	0.24	0.1		
14	M	22	17	0	0	0	0	0	0	0	+	0	+	0.2	0.2		
15	M	24	24	0	0	—	3	+	0	0	0	+	0	0.12	0.25		
16	F	24	20	0	0	+	3, 4	+	—	—	—	—	—	—	—		
17	M	27	27	0	0	0	3	0	+	+	+	0	0	0.24	0.5		
18	M	27	12	+	0	0	7, 8	0	+	+	+	0	0	0.24	0.3		
19	F	28	25	0	0	+	2, 4, 7	0	+	+	—	—	—	—	—		
20	F	28	23	0	0	+	2, 4	0	+	+	+	0	0	0.2	0.15		
21	F	28	28	0	0	+	0	0	+	+	+	0	+	0.18	0.1		
22	F	29	17	0	0	+	1, 2, 4	0	+	+	+	0	+	0.22	0.2		
23	M	32	24	0	0	+	0	0	+	+	—	—	—	—	—	Died, necropsy	
24	F	33	23	0	0	+	4, 7	0	+	+	+	0	0	0.16	0.25		
25	M	35	22	0	0	+	3, 7, 8	0	+	+	+	0	0	0.2	0.3		
26	M	35	34	0	0	0	0	+	+	+	0	0	0	0.18	0.25		
27	F	36	16	0	0	0	0	+	+	+	0	0	0	0.16	0.3		
28	F	38	35	0	0	+	0	+	+	+	0	0	0	0.2	0.2		
29	M	40	30	0	0	—	0	—	0	+	—	—	—	—	—		
30	F	41	37	0	0	0	7, 9	—	+	+	+	—	—	—	—		
31	M	41	41	0	0	0	1, 3, 4, 7, 8, 11	+	+	+	0	0	+	0.14	0.1	Died, no necropsy	
32	M	42	41	0	0	—	3, 9, 10	+	+	+	0	0	+	0.16	0.15		
33	M	43	43	0	0	0	3, 8, 9, 10	+	+	+	0	0	+	0.12	0.5		
34	F	44	24	0	0	0	4, 8	+	+	+	0	0	—	0.16	0.2		
35	F	47	47	0	0	0	0	+	+	+	0	0	0	0.2	0.2		
36	F	49	43	0	0	0	3, 7	0	+	+	—	—	—	0.14	0.1	Died, no necropsy	
37	M	53	53	0	0	0	3, 4, 7, 8	0	+	+	0	0	+	0.16	0.15		
38	M	55	55	0	0	0	3	0	+	+	0	0	+	0.12	0.5		
39	M	59	56	0	0	+	3, 4, 9, 10	0	+	+	0	0	+	0.16	0.2	Died, necropsy	
							3, 8, 10	0	+	+	0	0	+	—	—		
Totals	M 25 F 14	Av 30	Av 26	1	1	14	—	4	18	13	17	4	8				

\* +, positive, 0, negative, —, not known

† In "Other Infections" column 1, otitis media, 2, toothache, 3, smallpox, 4, measles, 5, chickenpox, 6, mumps, 7, malaria, 8, dysentery, 9, typhoid fever, 10, gonorrhea, 11, tuberculosis

‡ Lead I of electrocardiogram unsatisfactory

## NECROPSY FINDINGS

Of the six known deaths in our series three cases came to necropsy. In all of these the diagnosis of mitral stenosis was confirmed. The character of the stenosis in all three cases was that of a scarring as the apparent result of a chronic inflammatory process, with thickening of the valve flaps, thickening and shortening of the chordae tendineae and fibrosis of the papillary muscles and endocardium adjacent to the valve. The left auricle was hypertrophied and dilated in all three cases. In one patient (Case 35) a broken thrombus was found in the left auricle which may have been the cause of death. The aortic valve also was definitely distorted and stenotic in two of the three cases (Cases 23 and 35).

Table 5 gives in detail the joints dealt with in this paper.

## COMMENT

It has always been recognized that a certain number of cases of mitral stenosis have no clinical relationship to rheumatic fever or to any other definite infectious process. Such cases, however, have uniformly shown the same pathology at necropsy as cases in which there was definite association with rheumatic antecedents. The same is true of our cases, both clinically and pathologically. We cannot say, therefore, that these cases are not fundamentally the same as those occurring in association with rheumatic fever. They are apparently the result of some mild inflammatory process of a progressive nature which acts primarily on the most sensitive portion of the endocardium. It has never been established, however, that the so-called rheumatic endocarditis is caused by a specific micro-organism, although a nonhemolytic form of the streptococcus has been under suspicion. Our cases emphasize the obscurity of entrance and action of the infectious agent, whatever it may be, and call attention to the possibility that a variety of organisms or toxins may produce the same pathologic picture.

The scarcity of rheumatic fever in Peking is as striking as is the presence of mitral stenosis. We can offer no satisfactory explanation for this. Nowhere in China is rheumatic fever as prevalent as in America or England. Possibly more cases are seen in the damp climate of the Yangtze Valley than in the dry regions of North China, but even in Shanghai and Changsha only a few cases are met with. Certainly the climate is not a great factor in China, although Poynton and Paine<sup>5</sup> consider it so in England. Perhaps more important is a racial tendency of the Chinese to be less susceptible than occidentals to the type of pathologic change to which arthritis belongs. Arthritis

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<sup>5</sup> Poynton, F. J., and Paine, A. *Researches on Rheumatism*, New York, 1914, p. 392.

deformans, arteriosclerosis and gout are relatively rare among the Chinese. Whether this difference in susceptibility lies in the fact that the Chinese diet is primarily vegetarian, or whether some more intricate factors are responsible, we are not prepared to say.

#### SUMMARY

1 Mitral stenosis is the most common valvular disease of the heart in Peking, although rheumatic fever is very rarely seen.

2 Thirty-nine cases from the medical clinic of the Peking Union Medical College Hospital are reviewed. In the histories of these patients only one case of rheumatic fever, one case of chorea and fourteen cases of "joint pains" occurred.

3 No other infectious diseases appear to be especially involved in these cases of mitral stenosis.

4 In sex and age incidence, in electrocardiographic phenomena and in the pathology of three cases which came to necropsy, these cases are similar to the cases of mitral stenosis of rheumatic origin seen in Europe and America.



# THE CONCENTRATING CAPACITY OF THE KIDNEY \*

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A capacity for concentration must be conceded to the kidney, because most of the substances which it excretes are found to be in a state of higher concentration in the urine than in the plasma. The mechanism through which this concentration is accomplished cannot easily be conceived of as a process in which the kidney remains passive. It seems necessary to postulate that work is done by the renal tissue in converting a dilute plasma solution into a relatively concentrated urinary solution. On this account there has always been a special interest attached to observations dealing with the manner in which such an active function is affected by changes in the environment and structure of the kidney, though it must be admitted that there is as yet no unanimity of opinion regarding the factors which influence the renal concentrating capacity, nor any clear conception as to the method by which the concentration is produced.

Since 1909, when Ambard and Papin<sup>1</sup> published some data on this subject, the idea that there is a fixed upper limit to the concentrating capacity of the kidney for each urinary constituent has been widely accepted, and although it cannot be maintained that either their results, or the results of other authors which have since been published, constitute a proof that such maximum limits actually exist, it is at least the experience of all observers that certain high concentrations are rarely exceeded and then only under extreme conditions. This circumstance may be taken as an indication that the conditions under which these hypothetical limits are approached are those which are best adapted for an investigation of the factors which influence the concentrating capacity of the kidney. The general nature of these conditions is obvious from the fact that the concentration of any solid substance in the urine increases in direct proportion to every increase in the rate at which it is excreted, and decreases in direct proportion to every increase in the rate at which water is excreted. The highest concentrations are therefore to be expected when the rate of excretion of the substance in question is most increased and the volume of urine is at the same time reduced to a minimum.

Preliminary experiments were carried out in 1915, to obtain some general data with regard to the concentrating capacity of the kidney,

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1 Ambard and Papin Arch internat de physiol 8 437, 1909

and in particular to determine which of the various urinary constituents should be selected for special study. It was foreseen that at a later date we might wish to measure the effect which a change in the concentration of a substance in the blood might have on the concentration at which it was eliminated in the urine. This requirement excluded certain substances which might otherwise have been chosen, because the methods available for their determination in blood did not have the reliability necessary for our purpose. It was also necessary to choose those substances whose rate of excretion in the urine could be markedly increased. Urea, sodium chlorid, and sodium acid phosphate can all be taken in considerable quantity and in high concentration. They were given to normal persons whose urine volume had been decreased by abstention

TABLE 1—*Decrease in the Rate of Water Excretion, Combined with Increase in the Rate of Excretion of the Substance Studied*

Name	After 30 Gm of Urea in 15 per Cent Solution Urea, per Cent	After 10 Gm Sodium Chlorid in 5 per Cent Solution Sodium Chlorid, per Cent	After 10 Gm Sodium Acid Phosphate 4H <sub>2</sub> O in 5 per Cent Solution Sodium Acid Phosphate, per Cent
I	4.38	1.78	1.77
W	3.39	1.69	1.80
Mc	3.41	1.50	1.82
S	3.55	1.57	1.64
M	4.06	2.25	1.29
B	4.26	1.42	1.77
K	4.85	1.74	2.07
Sh	3.92	1.86	1.52
Average concentration	3.98	1.66	1.71
Average rate of water excretion	596 c c	364 c c	222 c c
Average rate of substance excretion	23.2 gm	6.04 gm	3.75 gm

from water, and who were taking a diet which was low in sodium chlorid and in water. Other details of the experiments are given in a previous paper.<sup>2</sup> Thirty grams of urea were given in the first experiment, 10 gm of sodium chlorid in the second, and 10 gm of sodium acid phosphate in the third. In each case the solid was dissolved in 200 c c of water and ingested at 8 p. m. The concentrations found in the twelve hours' night urine (8 p. m. to 8 a. m.) are given in Table 1.

These concentrations are high, and in some cases approach the highest that have been observed. But it will be noted that with this method, in which the conditions are designed to produce a concomitant reduction of urine volume and increase of excretion of solids, we were not successful in maintaining the urine volume at a minimum, for there is a wide difference between the 596 c c excreted when urea was administered and the 222 c c eliminated after phosphate ingestion. It seemed

<sup>2</sup> Addis T, and Foster, M. G. Specific Gravity of Urine, Arch. Int. Med. 30:555 (Nov.) 1922.

possible, therefore, that fluid restriction alone might be as effective as the combined procedure. The same group of persons was therefore placed under the same conditions except that no urea, sodium chlorid or sodium acid phosphate was given, and the 200 c c of water in which these substances had been dissolved was also withheld. In this experiment, the concentration of all three substances was determined in the twelve hours' night urine (Table 2).

These concentrations are all considerably lower than those observed when the rate of excretion of the substance studied was increased, even though the rate of water excretion was much less than after urea or sodium chlorid had been given. It was therefore concluded that both fluid restriction and the administration of the substance selected for investigation was advantageous in studying the concentrating capacity of the kidney.

TABLE 2—Decreases in the Rate of Water Excretion Only

Name	Urea, per Cent	Sodium Chlorid, per Cent	Sodium Acid Phosphate, per Cent
I	3.51	0.468	0.604
W	1.47	0.485	0.380
Mc	2.59	1.160	0.605
S	2.60	1.064	0.567
M	1.90	1.190	0.595
B	2.57	0.856	0.645
K	3.56	0.803	0.750
Sh	1.41	0.285	0.295
Average concentration	2.45	0.706	0.580
Average rate of water excretion	243 c c		
Average rate of substance excretion	5.40 gm	1.78 gm	1.28 gm

It will be noted (Table 1) that phosphate administration was followed by a urine volume which was even less than when no additional substance was given. On this account we carried out another experiment in which 10 gm of sodium acid phosphate ( $\text{NaH}_2\text{PO}_4 \cdot 4 \text{H}_2\text{O}$ ) was taken and in this case determined the urea and chlorid as well as the phosphate concentrations. We were only able to obtain the cooperation of three of the subjects of the former experiments, but in all other respects the results are comparable (Table 3).

In spite of the low urine volumes the urea and chlorid concentrations are not so high as in the experiments in which urea and chlorid were taken. At this point we were deflected from our original purpose by our interest in the cause of the decrease in the rate of chlorid excretion which followed the ingestion of phosphate. Under other conditions this phenomenon is more pronounced than in the experiments we have given here, but no satisfactory explanation was obtained up to the time when the work was interrupted by the war. However, one other experiment was carried through, with the original group of subjects, in order to find whether still higher concentrations might not be attained if we

reduced the urine volume by giving phosphate while at the same time the rates of excretion of urea, chlorid and phosphate were increased by giving a mixture of all three substances. We were afraid that vomiting might be produced if we gave full doses of sodium chlorid and phos-

TABLE 3—*Decrease in the Rate of Water Excretion with Simultaneous Increase in the Rate of Excretion of Sodium Acid Phosphate by the Administration of 10 Gm Sodium Acid Phosphate*

Name	Urea, per Cent	Sodium Chlorid, per Cent	Sodium Acid Phosphate, per Cent
I	2.49	0.880	1.77
K	2.49	0.736	2.07
Sh	1.85	0.637	1.52
B	2.76	0.851	1.80
Ba	2.94	0.465	2.09
L	2.21	0.556	1.54
Bo	1.65	0.592	1.89
D	1.16	0.552	1.67
Average concentration	2.19	0.66	1.79
Average rate of water excretion	227 c.c.		
Average rate of substance excretion	4.89 gm	1.51 gm	4.00 gm

phate, so 5 gm of each was given with 30 gm of urea, all dissolved in 200 c.c. of water. The concentrations we found are given in Table 4.

Under these conditions the average concentrations are lower than when each substance is given alone, and in the case of chlorid and phosphate are even lower than when no chlorid or phosphate was given, because the increase in the rate of water excretion which the

TABLE 4—*Decrease in the Rate of Water Excretion with Simultaneous Increase in the Rate of Excretion of Three Substances by the Administration of a Mixture of 30 Gm of Urea, 5 Gm of Sodium Chlorid and 5 Gm of Sodium Acid Phosphate*

Name	Urea per Cent	Sodium Chlorid, per Cent	Sodium Acid Phosphate, per Cent
I	4.00	0.863	0.655
W	3.70	1.165	0.450
Mc	3.15	0.450	0.468
S	3.27	0.878	0.526
M	3.82	1.030	0.591
B	3.70	0.440	0.626
K	3.35	0.884	0.580
Sh	3.65	0.379	0.459
Average concentration	3.58	0.761	0.544
Average rate of water excretion	618 c.c.		
Average rate of substance excretion	22.02 gm	4.64 gm	3.34 gm

mixture induced was greater than the increase in the rate of excretion of chlorid and phosphate. The conclusion that we then reached was that the optimum conditions for a study of the concentrating capacity of the kidney for any substance could be met by restriction of fluids, and administration of that substance alone in a solution as concentrated as possible.

These experiments have been given in detail, because the results have a bearing on certain theories as to the mechanism underlying the concentrating capacity of the kidney

One hypothesis which might be advanced would explain the difficulty which is experienced in obtaining concentrations which surpass a certain rather ill defined limit, and would also enable us to bring under one category the observed maximal concentrations of all urinary constituents. This conception has been expressed with the greatest clarity by Ambard<sup>3</sup> in the statement that the maximal concentrations for urea, sodium chlorid and glucose are approximately isotonic with one another. If this were an established fact it would be a basis for a generalization as to the limitation of the concentrations of substances in the urine. It would be plausible to suppose that the limitation consisted in the inability of the kidney to remove from the blood any more of a given substance when the osmotic pressure of that substance had surpassed a certain level in the urine, a level which was the same for all urinary constituents. But because this is a simple and satisfactory theory, it is all the more necessary to make sure that it is justified by the experimental observations. Ambard bases it on the fact that the highest concentrations of urea and sodium chlorid which he has ever found in the urine of man are 5.6 per cent and 2.2 per cent, respectively, and he quotes Bouchardat as authority for the fact that the concentration of glucose may rise to 14.3 per cent. Urea and sodium chlorid have about the same molecular weight but the glucose molecule is nearly three times heavier, so that when the percentage concentrations are expressed as gram mols per liter they become 0.925 for urea, 0.376 for sodium chlorid and 0.789 for glucose. But urea and glucose are nonelectrolytes, while sodium chlorid is largely dissociated, so that the osmotic pressure is greater than the number of molecules per liter in proportion to the degree of dissociation. An 0.736 molar solution of sodium chlorid at 37.5 C (99.6 F) is 90 per cent dissociated, so the osmotic equivalent in gram mols per liter is 0.677. The relative osmotic pressures of 5.6 per cent urea, 2.2 per cent sodium chlorid and 14.3 per cent glucose are thus 0.0925, 0.0677 and 0.0789. These values, however, seem to be too diverse to justify the conclusion that the maximum concentrations of urea, sodium chlorid and glucose are approximately equivalent, or at least the approximation is not sufficiently close to justify speculation based on the supposition that they might be equivalent. And it should be remembered that we have provisionally accepted Ambard's figures as being truly representative. But the 14.3 per cent concentration of glucose is certainly a very exceptional concentration, much higher than those which we have observed. The greatest glucose concentration

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3 Ambard. *Physiologie normale et pathologique des reins*, Paris, 1914, p. 44

found by Keith<sup>4</sup> was 78 per cent in experiments on dogs dehydrated by the intravenous injection of a very large amounts of concentrated glucose solution, conditions which appear to be ideal for producing the highest possible concentrations. Ambard and Papin<sup>1</sup> give concentrations for urea and sodium chlorid which they believed were maximal. They were obtained in dogs under special conditions, an exclusive meat diet for the urea experiments, and the injection of sodium chlorid or the giving of salted water for the sodium chlorid experiments. The osmotic values of the maximal concentrations were always much less for sodium chlorid than for urea. In the six dogs on which maximal concentrations for both urea and chlorid were obtained, the average osmotic pressure of the urea was equivalent to 1.049 molar while the sodium chlorid, after correction for dissociation, had a pressure equivalent to only 0.335. Therefore either these chlorid concentrations were not maximal or the rule of the uniformity of maximal osmotic pressure values which Ambard believes is followed in man does not hold for dogs. In general, it seems to us that Ambard's results do not at all justify his conclusion.

Adolph<sup>5</sup> has recently reported a large number of observations on himself in which varying but considerable amounts of urea, sodium chlorid and sodium bicarbonate dissolved in very little water were taken. He accepts the idea that there is a maximum concentration for each urinary constituent which the kidney cannot surpass and he concludes that this limit is the same for chlorid, phosphate, urea and bicarbonate, because he considers that the maximal concentrations of all these substances have approximately the same osmotic pressure. But in the first place there is no indication that any absolute maximum is ever reached. In the graphs, the concentrations rise in a curve and do not at any time take the form of a plateau. The urea concentrations which are called maximal vary in five experiments between 0.603 molar (3.65 per cent) and 0.828 molar (5.02 per cent). The sodium chlorid concentrations, corrected for ionization, vary from about 0.47 to 0.63 molar. This considerable range of variation is ascribed to a "daily variation concerned with the activities and water level of the entire body," to differences in the work of the kidney preceding the experiments and lastly to a "variation with long stretches of time, as from year to year." But in another experiment, in which he took no water for four days, still another maximum for sodium chlorid was reached, for under these conditions the corrected molar concentration of 0.662 was found. In the second place, the osmotic equality of the maximal concentrations of different substances is not demonstrated. The maximal concentrations

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4 Keith. *Am J Physiol* 63:394 1922-1923

5 Adolph, E. F. *Am J Physiol* 65:419 (Aug.) 1923

for urea and sodium chlorid are given as 0.678 molar and 0.522 molar (corrected for ionization), although no reasons are given why these particular figures should have been selected. In order to explain why the urea concentration is higher than the sodium chlorid concentration, it is pointed out that the difference between them, which is 0.156 molar, is approximately "the threshold concentration of sodium chlorid retained in the blood, and against this, of course, the kidneys have to work." But if it is right to add the sodium chlorid concentration of the blood to the chlorid concentration of the urine, why should the urea concentration of the blood not be added to the urea concentration of the urine? The blood urea concentration in normal persons rises to high levels after the administration of such large amounts of urea as were taken by Adolph, and if this had been taken into account there would still have been a discrepancy between the urea and chlorid concentrations. Only one experiment is given for sodium bicarbonate. The corrected molar concentration was 0.617, which is far from equivalent to the highest urea concentration of 0.828 molar. No data are given on phosphate concentrations.

During the last few years we have made a great many serial determinations of the concentration of urea in the urine after abstention from water or fluids for periods of from thirty to forty hours, combined with the repeated administration of considerable amounts of urea. In a few cases these experiments have been repeated many times on the same subject. The concentrations found were not dissimilar from those already reported by Ambard, Adolph and many others. The difference lies not in the facts but in their interpretation. Because it seemed to us quite apparent that the observed concentration might possibly have been surpassed if it had been feasible to continue the abstention from water still longer, we did not feel that we were justified in supposing that we had reached a "maximum" concentration in the sense in which that word is used by Ambard, i. e., "*une concentration que l'on ne pourra faire dépasser à l'animal par aucun procédé si artificiel soit-il*." This is the only adequate definition, because it is the only one under which maximal concentrations can be regarded as having any theoretic or practical importance. Our failure, and what we regard as the failure of others, to demonstrate the existence of any such maximum concentration does not permit us to conclude that there is no such thing, because in no case have the conditions required for the production of high concentrations been pushed to the ultimate limit. This, however, has now been done. MacKay and MacKay<sup>6</sup> report experiments which were specially performed to cause the greatest possible reduction in water available for excretion by the kidneys, and which were also accom-

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6 MacKay, L. L., and MacKay, E. M. *Am Jour Physiol* (in press)

panied by an increased rate of urea excretion. These conditions were maintained in some cases until the deprivation of water resulted in the death of the animal. Throughout the entire period the concentration of urea was determined in each collection of urine, and under these most extreme conditions these concentrations should at some time before the death of the animal have reached the "maximum" and thereafter have remained approximately constant. But in none of the sixteen animals used was the rising curve of the urine urea concentration converted into a plateau. Therefore, there is no such thing as a maximum urea concentration in the urine under conditions compatible with life. There is no limitation to the concentration of urea in the urine which is imposed by virtue of any incapacity of the kidney to produce a still more concentrated urine. If it were possible to induce conditions under which there would be even less water and more urea available for excretion, we have no reason to believe that the kidney might not respond with

TABLE 5—*Average Concentrations as Gram Mols per Liter, Corrected for Dissociation, Observed After Decrease in the Rate of Water Excretion Combined with Increase in the Rate of Excretion of the Substances Investigated*

Conditions	Urea	Sodium Chlorid	Sodium Acid Phosphate
Nothing given	0.480	0.250	0.087
Urea, 30 gm	0.665		
Sodium chlorid, 10 gm		0.505	
Sodium acid phosphate, 10 gm			0.242
Sodium acid phosphate, 10 gm	0.365	0.208	0.253
Urea, 30 gm, sodium chlorid, 5 gm, sodium acid phosphate, 10 gm	0.596	0.238	0.081

the production of a still higher urine urea concentration. This demonstration that the hypothesis of a maximum concentration which the kidney is unable to surpass is no longer tenable is of fundamental importance, because the general acceptance of this idea has led investigators to ascribe variations in the concentration of urinary constituents to changes in the concentrating capacity of the kidney. But if the full renal capacity is never reached, it is as logical to suppose that these variations may be due to changes in the environment of the kidney rather than to any supposed success or failure of the kidney in performing its work. If the difficulty which is experienced in obtaining very high urinary concentrations is not due to any inability of the kidney itself, it is as reasonable to suppose that it may be the result of the tenacity with which the various regulating mechanisms of the body resist more than a certain amount of deviation from the usual relations which are maintained between the water and the solids in the blood supplied to the kidney.

The hypothesis that "maximal" concentrations of urea, chlorid and phosphate, or rather such unusually high concentrations as may be



attained without too much discomfort to the subject of the experiments, have all approximately the same osmotic pressure may be tested from the experimental data we have given. The average percentage concentrations have been expressed as gram mols per liter, and in the case of the electrolytes, sodium chlorid and sodium acid phosphate, a correction for dissociation has been made from the measurements given by Shaeffer and Clover <sup>7</sup> and by Watkins <sup>8</sup>.

The osmotic equivalents of the highest average concentrations are 0.665 for urea, 0.505 for sodium chlorid and 0.253 for sodium acid phosphate. If we take the highest of all the observations we have 0.800 for urea, 0.674 for sodium chlorid and 0.317 for sodium acid phosphate. It cannot be maintained that there is even an approximate correspondence between these values and, as a matter of fact, when the various consequences which may be inferred from the theory of a limited renal concentrating capacity are no longer entertained, there does not seem to be any good reason to expect that they should be the same. There is, on the contrary, a reason to anticipate that phosphate concentrations might never become osmotically equivalent to high urea concentrations. For, given the same degree of decrease in water excretion, the concentration of that substance will be the highest whose rate of excretion can be most augmented. Now it is not possible to reach any limit to the capacity of the kidney in excreting either urea or phosphate. For when more and more is given the concentration of urea and of phosphate in the blood rises higher and higher, but the kidney continues to respond with an ever increasing rate of excretion, which in the case of urea tends to be directly proportional to the blood urea concentration,<sup>9</sup> and in the case of phosphate also varies in direct relation to the plasma phosphate concentration <sup>10</sup>. If, however, sufficiently concentrated solutions of either urea or phosphate are injected intravenously for a long enough time the muscles will begin to twitch, soon afterward there is a convulsion and the animal dies. Nevertheless, up to the time at which these symptoms appear the kidney is still smoothly and steadily increasing the rate of excretion in correspondence with the mounting blood concentration, so that the limit to the attainment of still higher rates of excretion is imposed, not by the kidney, but by the nervous system. This limit is set at a much lower level for phosphate than for urea. We have been unable to obtain rates of phosphate excretion which exceed 150 mg sodium acid phosphate hourly per kilogram of body weight without the development of these nervous disturbances, but with urea, rates as high as 1,785 mg hourly per kilogram of body weight have

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7 Shaeffer and Clover. *Carnegie Inst Wash*, 1912, No 170, p 14

8 Watkins. *Carnegie Inst Wash*, 1915, No 230, p 153

9 Addis, T, and Drury, D R. *J Biol Chem* 55 105 (Feb) 1923

10 Addis, Mayer and Myers. Observations (to be published)

been obtained<sup>11</sup> There is, therefore, reason to expect that phosphate concentrations in the urine cannot be increased to such a high level of osmotic pressure as is possible for urea, no matter how extreme the conditions may be The rate of sodium chlorid excretion is limited in much the same way, and possibly for the same reason that the rate of sodium phosphate excretion is restricted<sup>12</sup> On a *priori* grounds it is therefore improbable that high concentrations of urea, sodium chlorid and sodium acid phosphate will have the same osmotic pressure, for the inequalities in the maximum rates of excretion would have to be counterbalanced by proportional inverse changes in the rates of water excretion Certainly, under the conditions which have been investigated, even the results of those who have advanced the theory fail to demonstrate any equality between urea and sodium chlorid concentrations, and in the experiments which we have given a pronounced inequality between the molecular ionic concentrations of urea and phosphate has been found

There is still another hypothesis in which renal incapacity is regarded as the limiting factor in determining urinary concentrations under certain conditions Chaussin<sup>13</sup> found that "maximal" concentrations of urea could be obtained only when the rate of salt excretion was low, and similarly that "maximal" sodium chlorid concentrations were found only when the conditions were such that the rate of urea excretion was low He supposes, therefore, that the concentration of one substance is influenced by the concentration of other substances and since he found that the sum of the urea and chlorid concentrations was almost constant, he concludes that the kidney is limited in its capacity to secrete a urine whose total osmotic pressure exceeds a certain level "La charge de l'organisme en sel diminue la capacité du rein vis-à-vis de l'élimination de l'urée et réciproquement" Our own observations might be regarded as supporting this theory for the highest concentrations of urea, chlorid and phosphate were obtained only when each substance was given alone On the other hand, we failed to reach any limit to the total concentrating capacity of the kidney, for the total gram molar concentration, corrected for ionization, increased from 0.665 with decrease in water excretion, to 0.769 when urea, chlorid and phosphate were taken together However, if the kidney is really incapable of excreting high concentrations of urea and chlorid at the same time, its failure should become very manifest when the conditions are more rigorous than was possible in Chaussin's or in our experiments We accordingly gave urea and sodium chlorid by stomach tube to rabbits deprived of water The results are given in Table 6

11 Drury, D. R. *J. Biol. Chem.* **55** 113 (Feb.) 1923

12 Munzer *Arch. f. exper. Path. u. Pharmacol.* **41** 74, 1898

13 Chaussin *J. de Physiol. et de path. gen.* **18** 895, 1919-1920

It is evident from these results that the kidney is able to secrete urine in which the concentration of both urea and chlorid is high. But when the rate of excretion of urea alone is increased, the increased rate of water excretion which is associated with that increase will, of course, lower the concentration of chlorids, just as a marked increase in the rate

TABLE 6—Results of Administration of Urea and Sodium Chlorid in Four Rabbits

Rabbit 1, Weight at One Hundred and Twentieth Hour, 2,000 Gm					
Conditions	Time of Urine Collections, Number of Hours Without Water	Volume, Cc per Kilogram of Body Weight Hourly	Urea Percentage, Gm per 100 Cc	Sodium Chlorid Percentage, Gm per 100 Cc	
No water or food for 120 hours	?-120th		5.22	0.07	
	120-123d	12.7	3.00	0.41	
	123-126th	7.7	3.25	0.25	
	126-129th	3.3	4.92	0.26	
	129-132d	2.3	5.74	0.33	
	132-135th	1.8	5.75	0.49	
	135-147th	1.5	5.18	0.93	
At 147th hour 5 gm urea and 1 gm sodium chlorid in 20 cc water	147-151st	5.8	3.94	0.76	
	151-155th	3.4	5.42	0.82	
	155-159th	2.0	5.92	1.00	
	159-171st	1.2	6.12	0.65	
At 171st hour 1 gm sodium chlorid in 20 cc water	171-176th	0.5	2.70	0.82	
	176-183d	0.7	4.85	0.96	
Died soon after 183d hour	183-?		4.06	0.94	
Rabbit 2 Weight at Forty-Eighth Hour, 2,000 Gm					
No water or food for 48 hours	?- 48th		3.99	0.01	
At 48th hour 10 gm urea in 20 cc water	48- 55th	10.0	4.29	0.09	
	55- 70th	2.3	6.60	0.00	
At 75th hour 5 gm urea and 1 gm sodium chlorid in 20 cc water	70- 79th	4.4	5.59	0.51	
At 90th hour 5 gm urea and 1 gm sodium chlorid in 20 cc water	79- 90th	1.8	6.94	0.51	
Died soon after 111th hour	90-111th	3.6	5.28	0.66	
	111- ?				
Rabbit 3 Weight at Forty-Eighth Hour, 2,350 Gm					
No water or food for 48 hours	? - 48th		2.91	0.18	
At 48th hour 11.75 gm urea in 23.5 cc water	48 - 55th	9.7	4.05	0.23	
	55 - 70th	8.5	7.20	0.08	
At 70th hour 5.88 gm urea and 1.25 gm sodium chlorid in 23.5 cc water	70 - 79th	4.5	6.13	0.52	
	79 - 90th	1.0	6.78	1.00	
At 90th hour 5.88 gm urea and 1.25 gm sodium chlorid in 23.5 cc water	90 -111th	3.6	5.34	0.80	
	111 -123d	1.1	6.51	0.29	
	123 -134.5	1.1	6.36	0.26	
	134.5-148.5	0.8	6.74	0.01	
At 148.5 hour 5.88 gm urea and 1.25 gm sodium chlorid in 23.5 cc water	148.5-152.5	0.9	4.42	0.01	
Died at 152.5 hour					
Rabbit 4 Weight at Fifty-Fifth Hour, 1,900 Gm					
Conditions	Time of Urine Collections, Number of Hours Without Water	Volume, Cc per Kilogram of Body Weight Hourly	Urea Percentage, Gm per 100 Cc	Sodium Chlorid Percentage, Gm per 100 Cc	Acid Sodium Phosphate Percentage, Gm per 100 Cc
No food or water for 55 hours	?- 55th		4.04	0.00	1.56
At 55th hour 9.9 gm urea in 19 cc water	55- 70th	5.3	5.61	0.03	0.31
At 70th hour 4.99 gm urea and 0.99 gm sodium chlorid and 0.99 gm acid sodium phosphate in 19 cc water	70- 79th	4.7	6.27	0.21	0.83
	79- 90th	1.5	6.81	0.01	1.61
At 90th hour 4.99 gm urea and 0.99 gm sodium chlorid and 0.99 gm acid sodium phosphate in 19 cc water	90-103d	2.8	5.07	0.69	0.76
	103-115th	2.3	5.10	0.94	0.82
	115-126.5	0.2	2.69	0.01	0.46
Died soon after 126th hour					

of chlorid excretion will, as a rule, lead to a decrease in the urea concentration. Chaussin's findings may be explained on these grounds, and it is unnecessary to assume that the kidney is incapable of producing high concentrations of both simultaneously. Whether this is true for all urinary constituents it is impossible to say. There are certain effects on chlorid excretion produced by the administration of phosphate for which we have no explanation, but certainly the suggestion that they are due to renal incapacity seems to us more improbable than many others which might be given.

TABLE 7—*Association Between Rate of Water and Rate of Substance Excretion*

Substance = Urea			
Conditions	Water, Cc in 12 Hours	Urea, Gm in 12 Hours	Urea + Chlorid + Phosphate Gm in 12 Hours
Phosphate, 10 gm	227	4.89	10.40
Nothing	243	5.40	
Urea, 30 gm	506	23.20	
Urea, 30 gm, sodium chlorid, 5 gm, sodium acid phosphate, 5 gm	618	22.02	30.00
Substance = Sodium Chlorid			
Conditions	Water Cc in 12 Hours	Sodium Chlorid, Gm in 12 Hours	Urea + Chlorid + Phosphate, Gm in 12 Hours
Phosphate, 10 gm	227	1.51	10.40
Nothing	243	1.78	
Sodium chlorid, 10 gm	364	6.04	
Urea, 30 gm, sodium chlorid, 5 gm, sodium acid phosphate, 5 gm	618	4.64	30.00
Substance = Sodium Acid Phosphate			
Conditions	Water, Cc in 12 Hours	Sodium Acid Phosphate, Gm in 12 Hours	Urea + Chlorid + Phosphate, Gm in 12 Hours
Phosphate, 10 gm	227	4.00	10.40
Nothing	243	1.28	
Phosphate, 10 gm	222	3.75	
Urea, 30 gm, sodium chlorid, 5 gm, sodium acid phosphate, 5 gm	618	3.34	30.00

We have shown that the concentration of any substance in the urine is limited by the impossibility of increasing the rate of excretion of the substance beyond a certain point, without the production of symptoms which terminate in the death of the animal. If this were the only limitation the range of observed concentrations would be much wider than it is. But there is, of course, another factor to be considered, the rate of water excretion. Theoretically, the optimum conditions for the production of high concentrations consist in as great as possible an increase in the rate of excretion of the solid substance with at the same time, the maintenance of the rate of water excretion at a minimum value. But we found that whenever we succeeded in producing a marked increase in substance excretion we failed to keep the urine volume low. In Table 7, the average rates of water and substance excretion are given for all conditions.

If the water excretion when nothing was given is compared with the water excretion when each substance was given alone, it will be noted that the greatest increase occurs with urea, the substance whose rate of excretion was most increased. With sodium chlorid a moderate increase in rate of excretion is associated with a moderate rise in urine volume. With phosphate there was a slight decrease in volume but there was little increase in the rate of excretion, and there was at the same time some diminution in the rate of urea and chlorid excretion. There is, therefore, evidence of a relation between the excretion of solids and of water, and it seems likely that it is the total solid excretion which is related to the volume of urine, for in the experiments in which urea, chlorid and phosphate were all determined, the volume of urine varies in almost direct proportion to the sum of these three substances. It is evidently this tendency toward a parallel increase in water as well as in solid excretion, which is the real cause of the difficulty in obtaining very high urinary concentrations. It has been assumed that the water excretion is increased because the kidney is unable to excrete a substance at more than a certain maximum concentration. But since we have failed to find any evidence of any renal incapacity in concentrating it seems as reasonable to suppose that, under conditions in which the rate of excretion of any substance is markedly increased, the amount of water available for excretion may also be increased. The physical conditions within the body may be such that a pronounced increase in the concentration of any substance in the blood, which is the necessary precursor of any great increase in its rate of excretion, is inevitably accompanied by an increase in the concentration of free water in the blood. The absence of a very high concentration of any solid in the urine would then be only what was to be expected if the kidneys were efficient in eliminating together both solid and water, when their concentrations in the blood became greater than usual.

A very extreme instance of the relation between urea and water excretion is provided by experiments carried out in this laboratory by Drury<sup>11</sup>. By means of a Woodyatt pump, increasing amounts and concentrations of urea were injected intravenously into a rabbit anesthetized by chlorbutanol. A 0.9 per cent solution of sodium chlorid without urea was first injected at the rate of 27.3 c.c. hourly per kilogram of body weight, and then on different days 2 per cent urea at 27.3 c.c. hourly per kilogram of body weight, 2.5 per cent urea at 44.4 c.c. hourly per kilogram of body weight and finally 5 per cent urea at the rate of 78.3 c.c. hourly per kilogram of body weight. The concentrations of urea in the urine and in the blood and the rates of urea and water excretion are given in Table 8.

As the concentration of urea in the solution which was injected is increased to 5 per cent, there is no corresponding increase in the concen-

tration of urea in the urine Since we have often found concentrations of over 7 per cent in the urine of rabbits we cannot suppose that the kidneys of this animal were unable to produce a urine containing 5 per cent urea Nor is the relatively low urine urea concentration due to any falling off in the rate of urea excretion when the 5 per cent urea solution was injected, since the increase in the rate was at that time proportionally greater than the increase in blood urea concentration The 1.52 per cent concentration observed when 5 per cent urea was given was clearly due to an increase in water excretion, which was even larger than the increase in urea excretion When a rate of water excretion of 120.5 c.c. hourly per kilogram of body weight is obtained under conditions in which only 78.3 hourly per kilogram of body weight is injected, it would seem reasonable to look for some cause outside of the

TABLE 8—*The Effect of the Injection of Increasing Concentrations of Urea on the Concentration of Urea in the Urine When the Quantity of Urea Given Is Large Enough to Greatly Increase the Concentration of Urea in the Blood*

Solution Injected, Concentration of Urea	Urine Concentration of Urea, Gm. per 100 C.c.	Blood Concentration of Urea, Gm. per 100 C.c.	Urine Rate of Urea Excretion, Gm. per Kg. of Body Weight Hourly	Urine Rate of Water Excretion, C.c. per Kg. of Body Weight Hourly
0.0%	0.63	0.03	0.044	7.3
0.0%	1.14	0.03	0.041	3.6
2.0%	1.01	0.15	0.242	24.1
2.0%	1.71	0.17	0.210	12.3
2.0%	1.39	0.17	0.246	17.7
2.5%	2.16	0.32	0.669	30.9
2.5%	1.79	0.48	0.941	52.7
5.0%	1.52	0.76	1.827	120.5

kidney altogether, and the most likely explanation is, of course, that the injection of large amounts of a concentrated urea solution led to an increase in the concentration of free water in the blood This particular experiment is cited because it clearly shows the improbability of theories based on the assumption of renal incapacity For this rabbit excreted during the last period amounts of urea and water equivalent to an excretion by a man weighing 70 kg. of over 3,000 gm. of urea and of over 200,000 c.c. of water every twenty-four hours In view of this enormous capacity for work in elimination, very definite evidence should be required before the hypothesis of a renal incapacity to concentrate is seriously considered

As a general rule, the introduction of speculations in regard to the specialized function of the several components of the glomerulotubular element produces only a greater confusion in the consideration of the concentrating capacity of the kidney But in the case of urea we have very definite anatomic evidence of its existence in higher concentration within the cells of the proximal convoluted tubule than elsewhere in the

kidney or in the other tissues of the body. This was first shown by Leschke,<sup>14</sup> with the mercury method, and then by Oliver,<sup>15</sup> with the xanthidrol method. Oliver's results have since been fully confirmed by several observers.<sup>16</sup> As Oliver has pointed out, any hypothesis to account for this high urea concentration within these particular cells other than that they are actively engaged in excreting urea from the blood, entails highly improbable assumptions, and since the recent physiologic work of Marshall and Crane<sup>17</sup> leads to the same conclusion, it would seem that the theory that the excretion of urea is accomplished mainly by the proximal convoluted tubule is more firmly based on observed fact than are hypotheses in regard to the mode of excretion of other urinary constituents. But, though that part of the tubule may be the only place where a true secretion occurs, it seems likely that some urea passes with water through the glomerulus, and unless we assume an impermeability of the glomerulus for urea, or a special secretory activity of the glomerular epithelium for urea, for neither of which is there any evidence, we must suppose that the concentration of the urea which enters Bowman's capsule is identical with that which exists in the blood. Now, under ordinary conditions the urea which passes through the glomerulus may be insignificant in amount in comparison with the urea which passes in high concentration through the long proximal convoluted tubule, but, under the very extreme conditions of the experiment we have just cited, this glomerular fraction might become important. When it is remembered that a relatively enormous amount of fluid was being injected, and that life was only maintained by virtue of the ability of the kidney to excrete water at a very great rate, it seems unlikely that any appreciable amount of water which had passed into the lumen of the tubules from the glomeruli would be reabsorbed into the body again by the tubule cells. If this is granted, the volume of urine then becomes a measure of the greatest possible amount of water which could have been excreted through the glomeruli, the actual amount being less in proportion to the amount of water which may have passed through the tubule cells. And since we know the concentration of urea in the blood during each period of urine collection we can determine the amount of urea which may have been excreted by the glomeruli during a given time, and by subtracting this value from the total urea excretion we obtain the maximal possible glomerular rate of urea excretion and the minimal possible tubular rate of urea excretion. These values have been calculated from the data in Table 8 and are given in Table 9.

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14 Leschke *Ztschr f klin Med* **81** 14, 1915

15 Oliver, Jean *J Exper Med* **33** 177 (Feb) 1921

16 Stübel *Anat Anzeig* **54** 236, 1921 Piras *Arch de Fisiol* **20** 237, 1922 Walter *Arch f d ges Physiol* **198** 267, 1923

17 Marshall, E. K., Jr., and Crane, U. U. *Am J Physiol* **62** 330 (Oct) 1922

The results indicate that only a practically negligible fraction of the total urea excretion can pass through the glomeruli, even with large urine volumes, so long as the blood urea concentration is not markedly increased. But when the blood urea concentration rises to very high levels and at the same time the volume of glomerular filtrate is greatly augmented, the proportion of the total urea which is excreted by the glomeruli certainly becomes larger and larger until it might conceivably contribute almost half of all the urea eliminated under the unusual conditions of the last experiment. Now it has been demonstrated that under constant conditions the rate at which the same amount of renal tissue will excrete urea varies in direct proportion to the concentration of urea in the blood, so that the ratio  $\frac{\text{rate of urea excretion}}{\text{blood urea concentration}}$  is a constant.<sup>2</sup> These urea injection experiments were carried through in order to determine whether the kidney would be capable of excreting the very large amounts of urea which would be required if the relationship were

TABLE 9—*Calculated Rates of Glomerular and Tubular Urea Excretion per Kilogram of Body Weight*

Total Rate, Gm per Hour	Glomerular Rate, Gm per Hour	Tubular Rate, Gm per Hour	Blood Urea Concentration, Gm per 100 C c	Ratio	Total Rate Blood Conc	Ratio	Tubular Rate Blood Conc
0.044	0.002	0.042	0.027		1.63		1.56
0.041	0.001	0.040	0.027		1.53		1.50
0.242	0.035	0.207	0.149		1.63		1.29
0.210	0.020	0.190	0.166		1.27		1.14
0.246	0.031	0.215	0.174		1.41		1.25
0.669	0.117	0.552	0.377		1.77		1.46
0.941	0.254	0.687	0.482		1.95		1.43
1.827	0.909	0.918	0.755		2.42		1.22

to hold when the blood urea concentration was increased from about 25 to over 750 mg per hundred cubic centimeters. The results showed that the kidney did not fail even under this very great and unusual load, for the value of the ratio did not decrease, as would have been the case had the rate of urea excretion failed to increase in proportion to the increase in blood urea concentration. It will be noted that the magnitude of the ratio, which is given in the fifth column in Table 9, not only does not decrease, but that on the contrary, it becomes larger. This increase in the ratio in the last three experiments, when the blood urea concentration had risen to over 550 mg per hundred cubic centimeters, finds an adequate explanation in the actual inconstancy of the conditions which were such as to lead to an increasingly important increment of urea from the glomeruli, a source which does not follow any direct proportional relation to the blood urea concentration, since it varies also with changes in the volume of the glomerular filtrate. Although such considerations involve an element of speculation, they are supported by the fact that the ratios became approximately constant when the possible inconstancy in



the conditions is eliminated by calculating them in relation to the tubular rates instead of to the total rates of urea excretion<sup>18</sup> (Table 9)

The fact that there is no evidence that the kidney puts any restriction on the height to which the concentration of urea in the urine may rise gives us no right to assume that it may not limit the depth to which urine urea concentrations may fall. Knowing that urea is excreted by the proximal tubule in a higher concentration than that of the blood, and assuming that the glomerular filtrate has the same concentration as exists in the blood, it is clear that the lowest concentration of urea which can occur in the urine must be higher than the concentration of urea in the blood. The kidney would thus impose a limitation on the degree to which urea may be diluted in the urine, a limitation which would be a result of the mechanism adopted for the excretion of urea. But it may be that the elimination of urea is in reality more complicated than we suppose. There might, for instance, be a reabsorption of urea from the urine by the kidney, or at some part of its structure the kidney might be capable of excreting pure water without urea. If either of these two latter suppositions were correct, we might be able to obtain urine with a concentration of urea which was less than that present in the blood during the period in which it was produced. We have endeavored to induce the secretion of such a urine by injecting large amounts of salt solution or of water into rabbits, or by combining these injections with the administration of pituitary extract which decreases the rate of urea excretion,<sup>19</sup> but we never succeeded in reducing the concentration of urea in the urine below that of the blood. During the last ten years we have also made many synchronous observations of the urea concentration in the blood and urine of patients with uremia, but have always found a higher concentration in the urine than in the blood. While these negative results do not exclude the possibility of pure water excretion or of urea reabsorption, they at least indicate that there is no need to complicate a matter which is already sufficiently intricate by hypotheses which are unnecessary and on other grounds inherently improbable.

#### COMMENT

To anyone who has read this paper in the hope that some new facts might be presented which would at least make the subject more concrete,

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18 Addis and Drury (*J Biol Chem* 55 639, 1923), after many experiments on themselves, came to the conclusion that the rate of water excretion had no appreciable direct effect on the rate of urea excretion, but in this conclusion they overlooked the significance of the experiments we have discussed. In the exceptional circumstances of a very marked increase in both blood urea concentration and urine volume, any further increase in the rate of water excretion will cause an increase in the rate of urea excretion, because it will add an appreciable amount of urea through increased glomerular filtration.

19 Addis, Thomas, Barnett, and Shevky. *Am J Physiol* 46 52 (May) 1918

it will be apparent that the really fundamental questions have not even been approached. Such questions, however, cannot be formulated now, because the elementary facts of observation on which they will be based require methods for their determination which are not yet in existence. A first step, for example, is an exact knowledge of the concentrations which occur within the cells of the various sections of the glomerulo-tubular apparatus, but these concentrations will remain unknown until a quantitative histochemical method has been elaborated. But it will be admitted that, in our present state of ignorance, it is of some importance that no preliminary hypothesis should be accepted without thorough criticism, particularly if that hypothesis is used as a foundation for still other and wider hypotheses relating to renal physiology or if it is utilized in explaining functional deviations observed in patients. Ambard's views on this subject have been accepted and widely used, but we have tried to show that the facts from which they are derived can be coordinated under another hypothesis than his, one which is simpler and more in accordance with probability, and we have adduced still other facts which we believe make his position untenable. We maintain that at least the superficial aspects of all that we know about changes in the concentration of urea, chlorids and phosphates in the urine can be explained on the assumption that they duplicate parallel changes in the relation between the concentration of these solids in the blood and the concentration of the free water of the blood. We need not assume any incapacity on the part of the kidney itself in order to explain the difficulty experienced in obtaining very high concentrations in the urine. The experiments we have given do not reveal any such incapacity even under the most extreme conditions, and in any case it is an unnecessary assumption. We start with the knowledge that, by definition, the concentration in the urine depends on the relation between the rate of excretion of the substance and the rate of water excretion. Observation shows that when the rate of excretion of the substance is much increased there is also an increase in the rate of water excretion, and that this is the reason why the concentration of a substance in the urine never reaches a very high level. It is also a fact of observation that any marked increase in the rate of urea or of phosphate excretion is invariably accompanied by a marked and proportional increase in the concentration of urea and phosphate in the blood. In order to explain the increased water excretion which accompanies high rates of excretion and which keeps the concentration of urine from rising as high as it otherwise might, we assume that any pronounced increase in the concentration of the substance in the blood is associated with a parallel increase in the concentration in the blood of the free water which is available for excretion by the kidney. This assumption is not improbable on the basis of general physical analogy, but for the present it must remain an

assumption because no method has as yet been devised by means of which the concentration of free water in the blood can be measured. In a paper to be published, observations dealing with the cause of the low concentrations of urea found in the urine of patients in the terminal stages of Bright's disease will be given.

#### CONCLUSIONS

1 Experiments on normal human subjects are reported, in which the conditions were adjusted with a view to the production of urine which would contain the highest possible concentration of urea, chlorids and phosphates. It was found that the highest concentration of each of these substances was attained when it was given in considerable amount and in high concentration to subjects whose fluid intake had been restricted.

2 Experiments on rabbits deprived of water and given large amounts of a mixture of urea and sodium chlorid showed that it was possible to obtain urine in which there was a high concentration of both of these substances. No evidence was found which would suggest that the height to which the osmotic pressure of the urine might rise is restricted by virtue of any limitation in renal capacity.

3 The widely accepted hypothesis that the kidney is unable to excrete urea, chlorid or phosphates at more than certain maximum concentrations is shown to be untenable.

4 The assumption that concentrations of urea, chlorid and phosphate, which approach the highest levels found in the urine, have approximately the same osmotic pressure is shown to be contrary to observed facts.

5 It is suggested that changes in the concentration of urea, chlorids and phosphates in the urine are produced by changes in the relation between the concentration of these substances in the blood and the concentration of free water in the blood. It is difficult to obtain very high concentrations of the urine because a marked increase in the concentration of urea, chlorid or phosphate in the blood is associated with a concomitant increase in the concentration of free water in the blood.

# THE PRESENT STATUS OF THE QUESTION OF THE LENGTH OF LIFE OF THE UNAGGLUTINABLE TRANSFUSED RED BLOOD CORPUSCLE

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Isaacs,<sup>1</sup> in a recent publication from the Harvard Medical School and allied hospitals, has presented data which apparently establish a new and much needed means of identifying young red blood corpuscles. These cells which appear in the circulation after transfusion, can be distinguished by their content of one or more of four kinds of granules, of which the most important appears to be a comparatively large, non-staining refractile body. Isaacs has also quantitatively correlated the occurrence of granular and reticulated corpuscles to the presence of cells nonagglutinable with serum, containing isoagglutinins against the majority of the native cells of the circulation in question. So far as Isaacs' work concerns itself with the significance of the cells containing the refractile granule, I predict that it may prove a valuable contribution, but with respect to his conclusions concerning the tenure of life of the unagglutinable transfused corpuscle I do not agree.

Isaacs has made a modification of a technic which I introduced to follow the life of the Group IV (Moss) transfused corpuscle in the circulation of a recipient of another group, which is accomplished by agglutinating the recipient's corpuscles with Group IV serum and subsequently counting the remaining unagglutinated corpuscles in a hematocytometer. By means of the modification Isaacs considers that he has shown that the transfused unagglutinable corpuscles disappear and are replaced by unagglutinable young cells put into the circulation by the host. In the two published cases this replacement is complete in four days.

I consider that Isaacs has not proved his point for the following reason. The data in his two reported cases are in gross disagreement with my data in which forty-two cases were reported,<sup>2</sup> and with that

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1 Isaacs, Raphael. Properties of Young Erythrocytes in Relation to Agglutination and Their Behavior in Hemorrhage and Transfusions, *Arch Int Med* **33** 193 (Feb) 1924.

2 Ashby, Winifred. The Determination of the Length of Life of Transfused Blood Corpuscles in Man, *J Exper Med* **29** 267-281 (March) 1919, Some Data on the Range of Life of Transfused Blood-Corpuscles in Persons Without Idiopathic Blood Diseases, *M Clin N Amer* **3** 783-799 (Nov) 1919-1920, Study of Transfused Blood. I The Periodicity of Eliminative Activity Shown by the Organism, *J Exper Med* **34** 127-146 (Aug) 1921, Study of Transfused Blood. II Blood Destruction in Pernicious Anemia, *J Exper Med* **34** 147-166 (Aug) 1921.

of Wearn,<sup>3</sup> who also worked with this technic, both as to the number of unagglutinable cells found after a transfusion and as to the length of time that they are found in the circulation. The fact that like group transfusions do not produce an increase in the unagglutinable corpuscles offers a serious objection to Isaacs' conclusion that transfused Group IV corpuscles are replaced within four days by unagglutinable native cells. Moreover, his technic is open to certain objections.

The most serious obstacle to Isaacs' conclusion, that after four days the unagglutinable corpuscles found in the circulation are the young native cells which have replaced the transfused cells, seems to me to be the fact that it has already been shown by my data and also by that of Wearn that the like group transfusion does not produce this increase in unagglutinable corpuscles. As my data show that with the Group IV transfusion there is a sustained increase in unagglutinable corpuscles which is in proportion to the amount of blood transfused and the probable blood volume of the recipient, in order to meet this objection we would have to assume not only that the Group IV transfusion causes a prolonged stimulation of the bone marrow while the like group transfusion does not, but also that the stimulation was so adjusted that the number of new cells, produced as a result of the stimulation, consistently maintained the same relationship in all patients to the amount of blood originally transfused, and the blood volume of the recipient. Although this is theoretically possible, it is highly improbable, especially in view of the fact that I have found no difference in the subsequent effect of the two types of transfusion on the rise of the total red count.

In my own reported work are charted thirty-seven instances, and in the data of Wearn there are three, in which like group blood was transfused while the unagglutinable corpuscles were being studied, and practically no change in the count of unagglutinable corpuscles was found to take place following the like group transfusion. In Table 1, I am giving in detail the change in the count of unagglutinable corpuscles following a series of Group IV and like group transfusions in a single case (Case 57, already reported). The case was that of a man in Group II with pernicious anemia, which I have chosen because it offers an example of all the possible combinations: (1) an initial Group IV transfusion, (2) a Group II transfusion following a Group IV transfusion, (3) a Group II transfusion after a period of rest, (4) a Group IV transfusion following a Group II transfusion, and (5) a Group IV transfusion following a group IV transfusion. These combinations would seem to answer fully any questions that might arise as to whether the failure of unagglutinable corpuscles to appear in increased

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3 Wearn, J. T., Warren, Sylvia, and Ames, Olivia. The Length of Life of Transfused Erythrocytes in Patients with Primary and Secondary Anemia, *Arch Int Med* 29:527-538 (April) 1922.

numbers after a like group transfusion following a Group IV transfusion might be due to a change in the bone marrow activity resulting from stimulation. It will be seen that after each Group IV transfusion there is approximately the same marked rise, while after the like group transfusions the counts of unagglutinable corpuscles practically do not change (Table 1). In no instance, either in the studies of Wearn or in my reported forty-two cases, has there failed to occur a marked increase in the count of unagglutinable corpuscles following a trans-

TABLE 1—*The Failure of the Count of Unagglutinable Corpuscles to Increase After a Transfusion of Blood of the Same Type as That of the Recipient, and Its Invariable Rise After a Transfusion of Unagglutinable Blood*

(Case 57, Man, Group II)

Date	Count of Unagglutinable Corpuscles for Each Cubic Millimeter	Days After Transfusion	Difference Between Counts of Unagglutinable Cells Before and After Transfusion
5/20/19	0 011		
5/20/19	500 c c of Group IV eltrated blood transfused		
5/21/19	0 479	1	+0 468
5/26/19	0 488		
5/26/19	500 c c of Group II eltrated blood transfused		
5/29/19	0 466	3	—0 022
6/ 3/19	0 375		
6/ 3/19	475 c c of Group II eltrated blood transfused		
6/ 4/19	0 351	1	—0 021
6/ 9/19	0 383	6	+0 018
6/16/19	0 388		
6/16/19	500 c c of Group II eltrated blood transfused		
6/17/19	0 387	1	—0 001
8/ 4/19	0 208		
8/ 5/19	500 c c of Group II eltrated blood transfused		
8/ 6/19	0 181	1	—0 027
8/11/19	0 144	6	—0 061
8/11/19	0 144		
8/11/19	500 c c of Group IV eltrated blood transfused		
8/11/19	0 571	0	+0 427
8/13/19	0 500	2	+0 366
8/18/19	0 554	7	+0 110
8/18/19	0 554		
8/18/19	500 c c of Group IV eltrated blood transfused		
8/21/19	0 910	3	+0 396
8/22/19	0 940		
8/22/19	500 c c of Group II eltrated blood transfused		
8/26/19	0 840	4	—0 100

fusion with unagglutinable corpuscles, and in no instance, in which a like transfusion has been given, has there been found to be any change in the unagglutinable corpuscles, except of a slight degree such as might be accounted for by legitimate technical error, or, when there is a high count resulting from a previous Group IV transfusion, by probable change in blood volume. In my opinion this alone disproves Isaacs' contention.

Isaacs introduces an error into his calculations by computing the transfused corpuscles in terms of percentages of the total red count. Within a period of a few hours, provided that during that time no transfusion had been given, it would be fairly safe to assume that no change

in the absolute number of corpuscles in the circulation had taken place, and that any apparent change was due to blood volume fluctuations. Under these circumstances it would not only be permissible, but preferable, to base the percentage of the unagglutinable count on the total red count, as that would cancel the error due to any blood volume change. Over an extended time, however, such as these studies involve, it must be assumed that the native cells, which constitute the greater part of the total red count, are capable both of entering and of being removed from the circulation independently of the unagglutinable corpuscles. In Isaacs' second case, for instance, by the fourth day after transfusion, the total red count had increased from 1,000,000 to 2,400,000. By basing the change in the number of unagglutinable corpuscles on the total red count, he has introduced an error of approximately 140 per cent, which, of course, is too great to be permissible. The total red count and the count of the unagglutinable corpuscles, whether these are regarded as transfused cells or as young native cells, have no necessary relationship to one another, and unless within the small changes that may fairly be attributed to blood volume fluctuations, the total red count remains constant, any estimate of a change in the transfused corpuscles that is based on a percentage of the total red count is incorrect.

I have taken the liberty of transposing the percentages given in the two cases reported by Isaacs to counts for each cubic millimeter of whole blood, and have compared the results obtained by him with my published data, and that of Wearn, Warren and Ames. These are included in Table 2, which compares the count of the unagglutinable corpuscles found in the circulation after transfusion with the amount of Group IV blood transfused. In Isaacs' cases and in all of mine that were not emergency transfusions, is given the increase in the count of unagglutinable corpuscles resulting from transfusion over the initial count of unagglutinable corpuscles (Table 1). The initial count of unagglutinable corpuscles is the count of the few corpuscles which remain free after a pure blood of an agglutinable type has been treated with an excess of agglutinating serum. The number remaining free depends partly on the potency of the serum, and partly on a quality of the corpuscles which makes them more or less agglutinable. As corpuscles deteriorate *in vitro*, for instance, their agglutinability decreases and the number of free corpuscles found after agglutination becomes greater. Group III corpuscles have been reported to be, in some instances, weakly agglutinable. In any one subject I have found this initial degree of unagglutinability to be rather constant, but different subjects show considerable variation, as may be seen from Table 2. In cases of obstructive jaundice the agglutinability of the patient's corpuscles has been reduced, the clumps formed have been small and there has been

TABLE 2—*A Comparison of the Degree of Increase in the Count of Unagglutinable Corpuscles in Relation to the Amount of Unagglutinable Blood Transfused, as Obtained by Isaacs, with That Reported by Wearn, Warren and Ames, and by Ashby*

Diagnosis	Volume Transfused, Cc	Count of Unagglutinable Corpuscles, Millions			Days After Transfusion
		Before Transfusion	After Transfusion	Difference	
Cases reported by Isaacs <sup>1</sup>					
Secondary anemia	400	a 0 103	0 236	0 131	1
		b 0 103	0 273	0 158	2
		c 0 105	0 209	0 104	4
		Av 0 105			
Primary anemia	600	a 0 087	0 170	0 105	1
		b 0 053	0 096	0 027	4
		Av 0 069	0 055	-0 014	6
Cases reported by Wearn, Warren and Ames					
1 Primary anemia	575		0 536		5
2 Primary anemia	400		0 465		2
3 Primary anemia	250		0 238		3
5 Chronic nephritis	624		0 624		3
6 Acute nephritis	550		0 275		3
7 Nephritis	250	0 046	0 261	0 215	10
8 Nephritis (boy)	250		0 451		2
Cases reported by Ashby					
6 Hemorrhage	1,200	0 088	1 412	1 324	2
7 Secondary anemia	500	0 011	0 391	0 380	6
8 Exophthalmic goiter	500	0 012	0 495	0 483	5
99 Malaria	500	0 027	0 451	0 424	1
199 Hemorrhage	500	0 033	0 500	0 477	7
115 Secondary anemia	500	0 057	0 692	0 645	3
G Anemia (infant) <sup>1</sup>	250	0 054	1 190	1 146	5
51 Aplastic anemia	500	0 025	0 478	0 448	0
57 Primary anemia	500	0 011	0 488	0 477	6
43 Primary anemia (163 pounds)	400	0 012	0 260	0 248	4
54 Primary anemia	450	0 022	0 464	0 442	3
26 Primary anemia	460	0 023	0 369	0 346	6
71 Primary anemia	490	0 025	0 554	0 529	3
89 Primary anemia	500	0 027	0 628	0 601	3
103 Primary anemia	500	0 015	0 612	0 597	4
45 Primary anemia	500	0 045	0 570	0 525	4
91 Primary anemia	350	0 053	0 463	0 415	2
59 Primary anemia (short, fat)	400	0 069	0 713	0 644	6
61 Primary anemia	500	0 061	0 641	0 580	3
23 Primary anemia	500	0 080	0 642	0 562	5
23 Two years later	400	0 067	0 441	0 374	4
73 Primary anemia	500	0 086	0 454	0 368	5
80 Primary anemia	500	0 115	0 560	0 445	4
60 Primary anemia	500	0 170	0 693	0 523	4
68 Primary anemia (82 pounds)	500	0 229	1 196	0 967	3
21 Obstructive jaundice	500	0 154	0 670	0 526	4
55 Obstructive jaundice	500	0 220	0 720	0 500	3
47 Hyperthyroid	500		0 684		21
48 Cancer of breast	500		0 565		25
76 Secondary anemia	500		0 532		8
25 Obstructive jaundice	500		0 623		10
38 Hemorrhage	500		0 759		5
50 Hemorrhage	500		0 393		10
76 Secondary anemia	500		0 532		8
92 Colloid goiter (215 pounds)	500				15
92 Colloid goiter (215 pounds)	500		0 622		6
96 Malignant pelvic tumor	500		0 470		10
63 Hemorrhage	500		0 626		9
83 Carcinoma of kidney	500		0 512		4
95 Hemorrhage	500		0 422		4
107 Pernicious anemia	500		0 594		5
116 Purpura	500		0 555		5
C Carcinoma	500		0 698		5



a comparatively large number of free corpuscles before transfusion with the Group IV blood, as may be seen in Cases 21 and 55. In cases in which a series of transfusions have been given elsewhere previous to the examination of the blood, there is the possibility of the presence of surviving Group IV corpuscles. Usually the count of unagglutinable corpuscles before transfusion with an unagglutinable blood is below 70,000 corpuscles for each cubic millimeter of blood.

Case 4 of the eight cases presented by Wearn is not included in the tabulation. It was a transfusion of 300 c c of Group IV blood from a patient with pernicious anemia into another patient with pernicious anemia, who was in Group II. Since neither the initial count of the unagglutinable corpuscles nor the corpuscle content of the blood which was transfused was determined, no conclusion could be drawn from it. I included all of my published cases except those that are given as instances of the failure of transfused blood to remain in the circulation.

In all of my cases and, with the exception of Case 6, in all of Wearn's cases, there tends to be a 10 : 1 relationship between the number of hundred cubic centimeters of blood transfused and the number of millions of unagglutinated corpuscles for each cubic millimeter found in the circulation of the recipient as a result of the transfusion. This 10 : 1 relationship results when the recipient's blood volume is 5,000 c c, and the count of the transfused blood is 5,000,000. A smaller corpuscle count in the transfused blood would decrease the number of unagglutinable corpuscles found in the circulation, and increase the first figure of the proportion, a smaller blood volume of the recipient would increase the second figure. In most instances both of these factors have operated simultaneously, as the blood used for transfusion was diluted by citration, and the patients had a low blood volume.

In Cases 7, 26, 43 and 50, in which the counts after transfusion are exceptionally low, a consideration of the data at hand would indicate that this can be accounted for by the higher blood volume of the patients and the lower count of the blood transfused. That in these apparent exceptions there is a relationship between the unagglutinable corpuscles found in the circulation after transfusion and the probable blood volume of the recipient, soon becomes evident when a blood volume estimate is made from the degree of dilution of the transfused blood as it occurs in the circulation, and a blood volume percentage is deduced from it. This has been done in Cases 7, 26, 43 and 50, using the following

equation, the blood volume per cent =  $\frac{C}{U_2 - U_1} \times T$ , where  $T$  is the amount of blood transfused,  $C$ , the number of corpuscles in the transfused blood,  $U_2 - U_1$ , the difference between the count of unagglutinable

corpuscles before and after transfusion and  $W$ , the weight of the patient. The results are as follows. In Case 43 ( $W = 74$ ,  $T = 0.42$ ,  $C = 4.08$ ,  $U_2 - U_1 = 0.248$ ) the calculated blood volume percentage was 8.4. In Case 7 ( $W = 61.5$ ,  $T = 0.5$ ,  $C$  was assumed to be 4.5 as the blood was citrated and the donor was a man,  $U_2 - U_1 = 0.38$ ) the calculated blood volume is 9.7. In Case 26 ( $W = 70.5$ ,  $T = 0.46$ ,  $C = 4.53$ ,  $U_2 - U_1 = 3.46$ ) the calculated blood volume percentage was 8.5. In Case 50 ( $W = 69$ ,  $T = 0.5$ ,  $C$  was assumed to be 4.0 as the blood was citrated and the donor was a woman,  $U_2 - U_1 = 0.35$ ,  $U_1$  assumed to be 0.043) the calculated blood volume percentage is 8.3. These are within the blood volume percentages reported as normal by the vital dye method.<sup>4</sup> They would seem to be probable blood volumes for these cases even for the two cases of pernicious anemia (Cases 26 and 43), for these patients were fairly well in spite of a low red count and increases in plasma volume have been shown by Keith<sup>5</sup> to occur in cases of pernicious anemia which may more than compensate for the reduced corpuscle volume.

Applying the method of evaluating the counts of the unagglutinable corpuscles after transfusion by considering the possible dispersal of the blood transfused through the circulation of the recipient to the figures given by Isaacs<sup>1</sup> it will be found that they are abnormally small, even the first day after transfusion. In the first case<sup>6</sup> 400 c.c. of blood having a count of 5,000,000 was transfused. The patient weighed 50.2 kg., and the greatest increase in the number of unagglutinable corpuscles that appeared after transfusion was 158,000 for each cubic millimeter. In order that the transfused blood should be so diluted by the recipient's blood that the count of the transfused corpuscles should be as low as this, it would be necessary for the recipient to have a blood volume which was 25.2 per cent of her body weight. In the second case 650 c.c. of blood with a count of 6,000,000 was given. The recipient's body weight was 51.4 kg. and the increase in the count of unagglutinable corpuscles resulting from transfusion, was 105,000 for each cubic millimeter. These figures would indicate that the patient's blood volume was 75.5 per cent of her body weight. As these blood volume percentages are impossible, it is very evident that the blood corpuscles transfused are not accounted for by unagglutinable corpuscles found by Isaacs one and two days after transfusion, while in my observations,

4 Keith, N. M., Rowntree, L. G., and Geraghty, J. T. A Method for the Determination of Plasma and Blood Volume, *Arch. Int. Med.* **16**: 547-576 (Oct.) 1915.

5 Keith, N. M. The Total Circulating Volume of Blood and Plasma in Cases of Chronic Anemia and Leukemia, *Am. J. M. Sc.* **165**: 174-184 (Feb.) 1923.

6 Isaacs, R. Personal Communication.

and I judge in those of Wearn, the transfused blood can be quantitatively accounted for during many days, from fifteen to thirty after the transfusion

If Isaacs' technic is comparable to that used by Wearn and by me, his two cases must be abnormal, as an immediate elimination of transfused blood is indicated. If an error suggested by Isaacs in my technic, that of a retention of the sticky young cells in the tube in which the blood is allowed to agglutinate, is a factor, then the discrepancy between his two cases and the forty-eight presented by Wearn and by me, becomes greater instead of less.

Isaacs has changed the technic from a macroagglutination technic to a microagglutination technic. By the method, as I originated it,<sup>7</sup> a measured amount of serum and corpuscles was expelled into a Wassermann tube and shaken during the course of incubation to avoid inclusion of the unagglutinable corpuscles in the clumps formed. The time given was forty minutes with light shaking every ten minutes, but, as a matter of fact, agglutination is complete in a shorter time. After agglutination is complete, the free corpuscles are suspended by about twenty light shakes, and a sample is placed on the hemocytometer, and, immediately after settling, the count is made. By the modification of Isaacs, minute amounts of corpuscles and serum are measured, they are immediately placed on the counting chamber in which agglutination proceeds. By this method agglutination is not always complete in nine hours. Since the relative amounts of serum and corpuscles used by the two methods are comparable, this great lag in the procedure of agglutination must indicate that Isaacs has introduced a new factor. This might be the comparative lack of movement of the corpuscles, or it might be their tendency to adhere to the glass of the counting chamber to which they are greatly exposed. As the corpuscles have an opportunity to settle before they agglutinate, any of the young corpuscles described by Isaacs as sticky would necessarily stick where they settle, so that their failure to agglutinate would be evidence of their stickiness, but not necessarily of their unagglutinability. As by my technic I found low counts of 30,000 and 31,000 for each cubic millimeter of blood for the unagglutinable corpuscles before transfusion, in two cases of hemolytic jaundice, and as in the latter case the reticulocytes numbered 270,000 for each cubic millimeter of blood, I do not believe that the reticulocytes are intrinsically unagglutinable. Objection may be made to Isaacs' modification of the technic in that the insurance against inclusion of the unagglutinable corpuscles derived from transfusion in the clumps

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<sup>7</sup> Ice box incubation, which was included in the first description of the technic, was immediately retracted, as it was found to introduce irregularities attributed to false agglutination.

of the agglutinable corpuscles of the patient's blood has been removed, and in that it is not possible, by resuspension, to distinguish between the mechanical aggregation which tends to occur in some bloods, and true agglutination

Since by my technic I have not found these young cells of Isaacs or the reticulocytes among the unagglutinable corpuscles after a transfusion of unagglutinable blood, and have only found them in the residue of native unagglutinable cells in the same proportion in which they were present in the whole blood, I do not believe that they have been a factor in my data

The data on two unpublished cases which came under my observation, in which patients in Group I received Group II and Group IV transfusions, demonstrate that the type of the "unagglutinable cell" changes with the type of blood transfused. The blood of these patients, following Group II transfusions, in each case maintained its original agglutinability to Group IV serum, but there appeared and remained in the circulation for several weeks cells that were unagglutinable to Group II serum. One of these patients subsequently received a Group IV transfusion, which resulted in an immediate increase in the cells which were not agglutinable by Group IV serum. This increase was maintained for over two weeks. Since the type of the "unagglutinable cell" changed with the type of blood transfused, the possibility that these cells were derived from the host would seem to be ruled out.

So far as Isaacs' work with the blood of dogs is concerned, I do not consider that it is applicable to the question. The existence of isoagglutins in the blood of dogs is not established. By those workers who consider that they have found them they are admitted to be weak and inconstant as to type<sup>8</sup>. In my opinion they are unfit for separating mixtures of bloods.

#### SUMMARY AND CONCLUSION

Reasons are given, based on a large amount of data already published, which I consider prove that Isaacs is incorrect in his conclusion that "the use of agglutination in recognizing the cells of a donor in a mixture of two bloods in a transfused patient is of little value in from two to three days"

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<sup>8</sup> Ottenberg, R., Kaliski, D. J., and Friedman, S. S. Experimental Agglutinative and Hemolytic Transfusions, *J. M. Res.* **28** 144, 1913

# DETERMINATION OF THE RESISTANCE OF LEUKOCYTES \*

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## INTRODUCTION

Certain constant results have been reported and much interest awakened within recent years in the study of the fragility of erythrocytes. It is not expected that similar findings will prevail in work on leukocytes, which are regarded as approaching more nearly to typical human tissue in structure and function than erythrocytes.

Academically, the observation and measurement of particular reactions of leukocytes as an example of living tissue are of definite interest, but from the clinical standpoint special attention is aroused by the finding of certain reactions by Mauriac, Carbonat and Moureau that are claimed to indicate the prognosis of many diseases.

Mauriac, Carbonat and Moureau<sup>1</sup> have done the primary work of importance in the field of leukocyte fragility. An outline of their work follows.

Mauriac,<sup>2</sup> in 1916, devised a technic for the determination of the resistance of leukocytes by exposing blood to a hypotonic aqueous solution of 0.206 per cent sodium citrate and 0.3 per cent sodium chloride concentrations. He renewed the solution frequently because of the growth of molds. Three drops of blood were drawn into a Pasteur pipet and transferred into 0.5 cc of the before-mentioned solution. The mixture was then shaken and permitted to stand undisturbed for one hour. A clean slide was coated with a film of the suspended cells and dried for one-half an hour at room temperature. The preparation was stained, unfixed with saturated aqueous solution of methylene blue, washed gently in water and dried. The white cells were then counted.

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<sup>1</sup> This paper is No. 34 of a series of papers on the physiology and pathology of the blood from the Harvard Medical School and allied hospitals, a part of the expense of which has been defrayed by a grant from the Proctor Fund for the study of chronic disease.

1 Mauriac, P., Carbonat, P., and Moureau, M. *Compt rend Soc de biol* **22** 816, 1919; Moureau, M. *Recherches experimentales sur la fragilité leucocytaire*, Theses de Bordeaux **62** 8, 1919; Mauriac, P., and Moureau, M. *Compt rend Soc de biol* **83** 544, 1920.

2 Mauriac, P. *Ann de med* **3** 370 (July) 1916.

Mauriac was unable to differentiate the type of white cell by this method. The resistant ones appeared clean-cut in outline and the fragile cells hazy in form and pale blue. He established an arbitrary "Index of Fragility," namely, the number of resistant cells divided by the number of fragile cells. He found a decrease, or higher index, of fragility, with or without a leukocytosis in patients progressing to a favorable conclusion at certain critical periods in particular diseases, namely, immediately prior to (1) the clearing of the spinal fluid in cerebrospinal meningitis, (2) the clearing of the marked albuminuria and casts in the urinary sediment in nephritis and (3) the crisis in pneumonia. This diminution of fragility in cases presenting good prognosis he called an "Oscillation of Defense." Cases of typhoid fever, bronchitis, asthma and septicemia were likewise studied, but in these diseases the reactions were not so sharply defined as in the before-mentioned group. Other types of reactions than the "Oscillation of Defense" were observed. Mauriac found that an increased leukocyte fragility, as particularly noted in cases without an increasing leukocytosis, at any stage in a disease was an indication of poor general resistance and death frequently occurred. With each relapse of an infection, if the outcome was favorable, the fragility of the leukocytes fell, rising again gradually to normal as the patient recovered.

Mauriac, Carbonat and Moureau,<sup>1</sup> in 1919, utilized a slightly different technic in experimental work on the fragility of leukocytes. They noted very slight variation in normal rabbits. They constructed an index of fragility, namely,  $n \times 100/N$ , the "n" representing the number of fragile cells and the "N," the number of resistant cells. They employed the following technic: blood was drawn into a standard leukocyte counting pipet and diluted with an 0.1 per cent aqueous solution of sodium citrate, 0.05 per cent of sodium chloride and 0.02 per cent of methylene blue. The pipet was shaken and the cell suspension counted after a fixed period.

Three types of reactions were observed: (1) Succeeding the injection of turpentine, antidiaphtheric serum, typhoid vaccine or colloidal metals in rabbits, Mauriac's "Oscillation of Defense" was demonstrated in those animals which showed favorable progress, (2) succeeding the intravenous injection of neoarsphenamin a leukocytosis was observed accompanied by an *increased* fragility and the authors suggested some association of this phenomenon with certain arsphenamin reactions in patients, and (3) succeeding the injection of various bacterial cultures and toxins, in those cases in which an increased fragility persisted in accompaniment with a normal leukocyte count or a leukopenia, the outcome was invariably fatal. But in the instance of the primary increased fragility

shifting permanently to a diminished fragility, all other conditions being similar, the outcome was not always fatal

For certain reasons, to be outlined below, a modification of the methods utilized by Mauriac et al has been made and used in the observations reported in this paper. Since the findings generally agreed with those of the before-mentioned investigators, it is not believed that these modifications detrimentally affected the results

#### METHOD

A drop of blood is drawn into a leukocyte counting pipet to the mark "1," and the diluting fluid, consisting of 0.1 gm sodium citrate and 0.05 gm sodium chlorid to each hundred cubic centimeters of distilled water, is drawn up to the "11" mark. The pipet is gently rotated while the fluid is drawn up. It is not shaken, but slowly rotated while the mixture is blown into a test tube, of from 5 to 8 mm internal diameter and from 3 to 6 cm in length, which preferably has been lined with paraffin. The test tube containing the diluted blood is corked, preventing evaporation which would cause an alteration of the concentration, and is then gently agitated for one minute to insure an even distribution of the cells throughout the solution. It is then allowed to rest undisturbed for exactly two minutes more, during which period the same pipet is washed out with water and the barrel refilled to the point "1" with 9 per cent sodium chlorid solution. At the expiration of the total three minutes the 9 per cent sodium chlorid is blown into the solution, the entire mixture drawn once into the pipet and then expelled into the test tube. One drop of 10 per cent aqueous solution Niagara blue or 10 per cent trypan blue is then added to the contents of the tube, which is gently shaken once or twice and then recorked. A large drop of the solution is taken from the test tube, placed on a smooth glass slide and covered with a No. 0 or 1 thickness cover-slip which should not contain marked ridges or other irregularities and should measure from 1.5 by 1.5 cm to 2.5 by 2.5 cm. The preparation is then rimmed with melted paraffin. The relative number of stained and unstained granular and nongranular white cells is counted in the proximal, central and distal portions of the preparation, running from one margin to the other of the cover-slip. The counting is completed within fifteen minutes from the time that the blood is diluted. Fragile cells have diffusely blue stained nuclei and the resistant cells are colorless and refractile. The counting of from two to three hundred white cells is facilitated by the ability to disregard erythrocytes through their early laking. The resistant and fragile white cells are distinctive, and one difficult to classify is very rarely encountered, actually less than 1 per cent.

## COMMENT ON METHOD WITH FACTORS CAPABLE OF INCREASING THE EXPERIMENTAL ERROR

It is appreciated that with the utilization of whole blood, many variable factors are introduced, some of which are later shown to have some appreciable effect in varying the number of fragile leukocytes by the method outlined in the foregoing. So far as present methods have progressed, it is apparently impossible to obtain pure leukocyte suspensions by the method of obtaining erythrocyte suspension without an indeterminate amount of trauma. The magnitude of this factor of trauma was demonstrated in an attempt to make such a leukocyte cream. Citrated blood was centrifugated in tubes with long, narrow necks so that a relatively high column of leukocyte cream was formed. This was pipetted off and suspended in Locke's solution. While this suspension was practically free of serum and erythrocytes, although not free of platelets, there were variable numbers of white cells injured prior to any exposure to hypotonic solution as determined by the diffuse staining of such cells by 1 per cent aqueous Niagara blue solution. The tendency to an increase of the susceptibility of the apparently uninjured cells to hypotonicity was a definite possibility not determined here, but presenting another variable factor.

Pappenheimer<sup>3</sup> showed, in his work on rat lymphocyte suspensions, that certain colloids had a protective action on the cells when exposed to hypotonic Locke's solution. Table 4 summarizes the work that was done by me with 1 per cent gelatin, Niagara blue, and acacia, in hypotonic sodium chlorid solution. In these experiments on human blood cells, gelatin and Niagara blue were active in the prevention of the destruction of cells in the hypotonic salt solutions. Pappenheimer included serum among the protective substances. By assuming a parallel situation *in vivo* it is possible that individual fluctuations in the proteins of the blood may be important factors, causing irregular determinations in investigations on the fragility of leukocytes which are not freed from erythrocytes and plasma. The control of the exact influence which these factors have on the fragility determinations must be left for future investigation.

The cell reactions to a hypotonic solution are complex phenomena depending on (1) the constituency and permeability of the cell membrane, (2) the difference in osmotic pressure of the solution and the protoplasm, and (3) certain other factors of vitality of the individual cell such as possibly a variation of the expansibility of the cell membrane causing it to burst at a certain point of distention. Much work has been done by Osterhout, Lillie, Overton, Loeb, Kuhne (quoted from

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3 Pappenheimer, A. W. *J. Exper. Med.* **25** 633 (May) 1917



Bayliss <sup>4</sup>) and others, in the determination of the general properties of protoplasm and cell membranes. As in the instances of the erythrocyte fragility, it is assumed that there are undetermined vital factors of resistance which are variable. Such factors may eventually be explained on the basis of known physical and chemical properties in which the resistant and the fragile cells differ. Such may be compared to the way in which other processes, as, for example, the fertilization of ova, formerly explained by purely "vital" factors, have been partially established on a definite physical or chemical basis.

The succeeding technical factors discussed, namely, physiologic balancing of a solution, toxicity of the anticoagulant, and trauma, are apparently well controlled by their exact duplication with each leukocyte fragility determination, and may therefore be disregarded in comparison of various results in which the same technic is employed.

1 For simplicity a solution of sodium citrate in a solution of sodium chlorid has been used, even though this introduces injurious influences other than those involved in the use of a physiologically balanced hypotonic solution. Ringer,<sup>5</sup> Locke<sup>6</sup> and others have shown the importance of a balanced solution in the maintenance of living tissue, and Pappenheimer showed that fewer lymphocytes were destroyed by exposure to hypotonic Locke's solution than in dilute sodium chlorid.

2 Unger,<sup>7</sup> Drinker<sup>8</sup> and others have shown the existence of a slight toxicity for human cells of dilute sodium citrate solutions. It is one of the least toxic of anticoagulants, however, and is here used in the minimum concentration, namely, 0.2 per cent, to prevent clotting (Mauriac, Carbonat and Moureau<sup>1</sup>).

3 The amount of handling and the kind of instruments used must be constant. Evans<sup>9</sup> has shown that very slight mechanical trauma destroys living cells in vitro. Having minimized the trauma, the standard is carefully maintained.

The percentage of sodium chlorid in the diluting solution, namely 0.5 per cent, agrees with that of Carbonat, Mauriac and Moureau. This percentage was determined independently in the present work, as shown in Table 1. The objective in fixing this sodium chlorid concentration was the establishment of a normal ratio of injured to uninjured cells. This ratio should shift in either direction to a maximum degree with

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4 Bayliss, W. M. Principles of General Physiology, New York, Longmans, Green & Co., 1920, chapter V.

5 Ringer, S. J. *Physiol.* **4** 222, 1882-1883.

6 Locke, F. S. *Zentralbl. f. Physiol.* **15** 490, 1901.

7 Unger, L. J. The Deleterious Effect of Sodium Citrate Employed in Blood Transfusion, *J. A. M. A.* **77** 2107 (Dec. 31) 1921.

8 Drinker, C. K., and Brittingham, H. H. The Cause of the Reaction Following Transfusion of Citrated Blood *Arch. Int. Med.* **23** 133 (Feb.) 1919.

9 Evans, H. M. Personal communication.

abnormal specimens The time of exposure of the cells to the solution should be long enough for convenience in handling and short enough to precede the disintegration of the dead cells Three minutes' exposure and a solution of 0.05 per cent sodium chlorid was considered the optimum ratio

Hypotonicity offered an ideal injuring medium, from the standpoint that the duration of its activity may be easily controlled At the end of the desired period, to the amount of one-tenth of the total volume of the solution, 9.0 per cent sodium chlorid was added by measuring it in the barrel of the same white cell pipet This brought the entire concentration of sodium chlorid to approximately 0.9 per cent This is recognized as approximately isotonic for human tissue, and in such a solution it was found that a sealed blood cell suspension did not alter in per-

TABLE 1—*Factors Determining the Destruction of Leukocytes with Hypotonic Solutions Effect of Time at Various Concentrations of Sodium Chlorid in an 0.1 Per Cent Sodium Citrate Solution*

Concentration of Sodium Chlorid, per Cent	Percentage Destroyed in							
	3 Min	5 Min	10 Min	15 Min	20 Min	30 Min	40 Min	60 Min
0.0	88.4	93.0	96.5	100.0				
0.02	90.0	94.0	97.0	100.0				
0.04	75.6	90.2	92.4	93.4	97.0	100.0		
0.05	50.0	67.8	84.4	81.7	89.8	92.6	100.0	
0.06	44.0	65.6	69.9	72.8	76.0	81.2	81.2	82.5
0.08	28.4	39.6	40.5	48.1	57.5	62.4	66.0	
0.10	28.0	32.4	34.6	38.7				67.2

The range of experimental error, as may be noted from fluctuation in counts on the same normal (Table 6), is greater than the apparently negative variations in Table 1, i. e., 0.05 per cent in 10 minutes and 15 minutes

centage of injured cells over 3 per cent in two and a half hours Leukocyte pipets furnish a ready source of accurate measurement of these small volumes, although at no time in this technic is the pipet used, as in blood counts, for shaking and distributing the cells because of the unquestioned trauma which the glass bead would inflict

Nontoxic dyes, such as Niagara blue or trypan blue,<sup>10</sup> are desirable These dyes readily stain the nucleus of injured or dead cells The dense, diffuse staining of a cell nucleus is a fairly well accepted criterion of fatal injury of a cell These benzidine dyes stain vitally only to a slight degree, if at all, and are so relatively nontoxic that they may be added in a concentrated aqueous solution Thus, only a small volume of dye solution is necessary, in order to have an effective content of dye in the entire mixture for the rapid staining of cells without increasing the volume appreciably The only disadvantage encountered in increasing the total volume of the mixture is dilution of the cell suspension which would prolong the period of counting

The chance irregular distribution on slightly ridged slides and cover-slips of cells whose elasticity, power of adhesion and size unquestionably differ markedly, necessitates the counting in several regions of the preparation. The importance of not injuring the cells through evaporation and increase of the concentration of the solution necessitates the sealing of the preparation by petrolatum, or preferably melted paraffin. The solvents necessary to remove petrolatum or paraffin from glass dissolve the cement in most types of counting chambers, which precludes the routine use of these in place of plain slides.

All the glassware must be scrupulously cleansed in distilled water and dried prior to using, since small deposits of sodium chlorid and probably other soluble substances will materially affect the final results. The sodium chlorid and sodium citrate diluting solution must be kept on ice when not in use and renewed once a month.

Three factors liable to affect the destruction of the cells were investigated in the following brief experiments.

TABLE 2—*Effect of Temperature Variation During the Exposure of the Blood to the Hypotonic Solution*

Temperature, C	Percentage of Cells Destroyed with Hypotonic Solution, per Cent	Percentage of Cells Destroyed with 0.9% Sodium Chlorid Solution (Control), per Cent
12	32	0.5
24	50	1.0
35	85	0.0
45	95	0.0

1 *The Effect of Temperature*—The glassware and solutions were brought to the temperatures noted in Table 2 and the technic carried out at these four temperatures. The increase of cell injury with higher temperatures was definitely observed. Therefore, to be comparable, all determinations of leukocyte fragility should take into consideration temperature variation.

In the following determinations on both normal and pathologic cases, the temperature of the room in which the tests were made varied within a few degrees of 25 C.

2 *Effect of Hydrogen-Ion Concentration of the Diluting Solution*—The concentration of sodium ions and chlorine ions was kept approximately at 0.05 per cent but the  $p_H$  was varied by the admixture of sodium hydroxid and hydrochloric acid. The results in Table 3 show a relatively slight variation, with the minimum fragility demonstrated in solutions of hydrogen-ion concentration from  $p_H$  7.6 to  $p_H$  8.4. After the addition of blood the mixture was necessarily buffered and consequently not the  $p_H$  noted in the table, for example, diluting solutions of

$p_H$  8.4 and  $p_H$  6.4 when mixed with blood ( $p_H$  7.45)<sup>11</sup> in the proportion before mentioned gave final determinations of  $p_H$  8.17 + and  $p_H$  6.57 + as determined by the electrometric method

It has been observed that the  $p_H$  of the diluting solution would change on long standing in ordinary glassware from 6.8 to 8.3. It is therefore necessary to keep the diluting solution in a flask of hard glass, or one lined with paraffin

TABLE 3—*Effect of Varying the  $p_H$  of the Diluting Hypotonic Solution*

$p_H$ *	5.6	5.8	6.2	6.6	6.8	7.0	7.2	7.4	7.6	8.2	8.4
Percentage of cells destroyed	56.0	52.0	52.0	54.5	48.5	54.5	50.0	48.5	42.0	38.0	38.0

\* By indicator dye method

Electrometric determinations of the  $p_H$  of the blood solution mixtures when, for example, the hypotonic diluting solutions were 8.4 and 6.4, was respectively 8.1 and 6.6. These two solutions of  $p_H$  8.4 and  $p_H$  6.4 were additional solutions not used in the foregoing series and therefore  $p_H$  6.4 does not appear in this table

3 *The Protective Action of Certain Colloids* (Table 4) —It was first found that if 1 per cent Niagara blue was added to the blood at the same time as the diluting solution, only from 20 to 25 per cent of the cells would be injured, instead of approximately 50 per cent, although the actual concentration of the sodium chlorid was diminished by the increase of the total volume

This phenomenon suggested my repetition of Pappenheimer's work on the protective action of certain colloids, which has been previously discussed, and is summarized in Table 4

TABLE 4—*Effect of Certain Colloids in Protection of Leukocytes from Destruction by a Hypotonic Solution*

	Percentage of Cells Destroyed with Three Minute Exposure on Two Different Days (a) and (b)					
	Gelatin		Acacia Gum		Niagara Blue	
	a	b	a	b	a	b
	Per Cent	Per Cent	Per Cent	Per Cent	Per Cent	Per Cent
Standard hypotonic solution containing 1 per cent of the colloid	36	29	46	44	26	22
Standard hypotonic solution (control)	48	51	48	49	48	51

A similar protective action of a foreign substance was assumed in the following observation

In using solutions from paraffined flasks, kept at room temperature for one week, there was a drop of from 54 to 36 per cent of fragile cells in the resistance determinations on the same blood, at the beginning and at the end of the week, respectively. In this solution a heavy

<sup>11</sup> Clark, W. M. Hydrogen-Ion Concentration, Baltimore, Williams & Wilkins, 1920

growth of bacteria, largely of the *B fecalis-alkaligenes* type, was found. Therefore, it was assumed that the actual bacteria or the products of their growth had a definite protective action.

The effect of the two before-mentioned factors, namely, hydrogen-ion concentration and protective action of growing bacteria, was proved by the entire absence of change in the destructive power of the solution when kept in paraffin lined flasks, which were constantly maintained in a refrigerator at about 10 C.

#### DETERMINATIONS ON NORMAL AND PATHOLOGIC BLOOD

Mauriac was unable to demonstrate by his technic the ratio of the various types of leukocytes destroyed. It is obvious that in certain instances the resistances of the different types of white corpuscles would be at variance. It is believed with the use of the technic herein outlined that, with moderately careful inspection, both in the case of the resistant forms and of the fragile forms, the coarsely granular myeloid cells may be differentiated from the finely granular lymphoid and large mononuclear cells. In two healthy men the ratios of coarsely granular cells to finely granular cells, among the resistant cells and the fragile cells of the same preparation, agreed very closely. Likewise, these were approximately the same ratios as the number of myeloid to other cells in Wright's stained smears of the same blood (Table 5). Similar determinations were made on one case of lobar pneumonia and on one of

TABLE 5—*Normal Ratio of Coarsely Granular Myeloid Group to Finely Granular Large Mononuclear and Lymphoid Cells in the Fragile and in the Resistant Cells of Two Normal Adults*

Case	Resistant Cells, per Cent	Fragile Cells, per Cent	Total Leukocytes (Fixed Blood Film) per Cent
1 {Myeloid	64	62	65
{Other cells	36	38	35
2 {Myeloid	58	62	66
{Other cells	42	38	34

chronic lymphatic leukemia, but in both these instances, as in the two controls, it was impossible to demonstrate a selection of a particular group of cells as being less resistant than the other.

The establishment of what is to be considered the figures for the percentage of fragile leukocytes has been only partially accomplished, as may be gathered from the rather wide variations obtained. Table 6 summarizes the findings on normal subjects. The subjects used were eighteen healthy adults, thirteen men and five women, between the ages of 21 and 35. Apparently from 45 to 55 per cent of fragile cells may be considered the normal average, with 43 and 63 per cent as the extremes. Daily and hourly fluctuations were observed in two subjects,

Cases 1 and 2, but the cause of these individual fluctuations is still to be learned, and perhaps may be associated with such total leukocyte fluctuations as occur following the taking of food

TABLE 6—*Determinations of Percentage of Fragile Cells in Normal Adults, Utilizing the 0.05 Per Cent Sodium Chloride—0.1 Per Cent Sodium Citrate Solution with Three Minute Exposure*<sup>†</sup>

Case	Sex	Percentage of Fragile Cells
1	♂	70 determinations, minimum, 44%, maximum, 62%, daily fluctuations within 10%, only 8 determinations were above 55% or below 46%
2	♀	54, 47, 52
3	♀	53
4	♀	58
5	♀	60
6	♀	45
7	♀	43
8	♀	55
9	♀	49
10	♀	58
11	♀	52
12	♀	49
13	♀	53
14	♀	51
15	♀	51
16	♀	53
17	♀	52, 54
18	♀	55

\* Repeated determinations were made on different days except in several of the determinations in Case 1

† In this column, ♀ indicates female, ♂ male

Table 7 shows the pathologic cases studied. In the cases of pernicious anemia the fragility tended to vary inversely with the hemoglobin. The exception to this is Case 1, whose low resistance may be interpreted as a prelethal phenomenon.

With the leukocytoses due to infection especially, as shown in the pneumonia cases, there occurs an increased resistance of the recently extruded and relatively young leukocytes which the healthy blood-forming organs have sent out. This is Mauriac's "Oscillation of Defense," and whereas the leukocyte resistance has not been traced throughout the course of the disease, its subsidence with recovery in the Cases 12 and 13 indicates that it probably follows the same curve as Mauriac has traced and found to vary inversely as the absolute leukocyte count. It is especially important to note, as suggesting negative evidence in the use of leukocyte fragility as an aid in determining prognosis, that the two fatal cases showed an increased resistance when compared to the normal cases, and as such may be said to have had an "Oscillation of Defense." However, it is definitely demonstrable that none of the pneumonia patients recovering, showed a fragility of over 30 per cent cells destroyed, while both of the fatal cases gave a greater percentage of cells destroyed. It must therefore be considered possible

to fix an arbitrary normal fragility for certain diseases with certain degrees of leukocytosis, which, if exceeded, will in all probability be indicative of a poor prognosis

TABLE 7—*Leukocyte Fragility in Adults with Certain Diseases*

<i>A Cases of Pernicious Anemia</i>					
Case	Percentage Fragile Cells	Hemo globin, per Cent	Erythrocyte Count, per C Mm	Leukocyte Count, per C Mm	Miscellaneous Features
1	89.7	15			One day prior to death (no evidence of blood regeneration at this time)
2	66.0	30	2,100,000	4,300	
3	60.0	40			
4	52.0	24			
5	50.0	18	848,000	3,700	Blood film shows 14% fragmented white cells
<i>B Cases with Secondary Anemia</i>					
6	27.0	40			Post hemorrhage
7 1st day	24.0	50			Sudden anemia after aspidium ther- apy for <i>T. saginata</i> , blood crisis with 14,000 per c mm nucleated red cells, 30% reticulated forms and many immature white cells
3d day	26.0				
5th day	38.0				
7th day	42.0				Gradual clearing of malaise with diminishing numbers of immature red cells in ten days though little change in hemoglobin
9th day	45.0	60			Continued improvement
<i>C Cases of Leukemia</i>					
Case	Percentage Fragile Cells	Hemoglobin, Total per Cent	Leukocyte Count	Miscellaneous Features	
8	75.0	45	150,000	Acute myelogenous leukemia (?)	
9	22.0		86,000	Chronic myelogenous form in leukemic phase	
(one month later)	27.0		4,800	Aleukemic phase	
10	34.0	45	1,280,000	Chronic lymphoid leukemia	
<i>D Cases with Leukocytosis</i>					
11	27.0	40	19,800	Nephritis, subacute	
12 1st day	18.0	80	31,400	Lobar pneumonia	
3d day	18.0	80	20,400		
6th day	48.0		16,800	During lysis	
14 1st day	22.0	80	10,000	Lobar pneumonia (resolving)	
2d day	28.0				
4th day	40.0		8,200	After crisis	
14	39.0	85	17,800	Lobar pneumonia complicated by mis- carriage, death succeeding second day	
15	32.5 (75% myeloid type, coarsely granular)	80	19,800	Lobar pneumonia, death on succeed- ing day	
17	17.0	90	24,000	Lobar pneumonia, eventual recovery	

The two instances of secondary anemia, Case 6 due to hemorrhage, and Case 7 probably due to a hemolytic toxin, showed the increased resistance expected with the content of recently extruded and probably relatively young cells in the blood stream. This is better shown in Case 7 than in Case 6, wherein a gradual return to normal occurred concomitant with the fall in numbers in what are recognized as young forms of erythrocytes, namely, reticulated cells.

The two patients with a chronic type of leukemia demonstrate the same reaction as the infection leukocytoses, as would be expected from their exhibition of largely mature cells in the peripheral blood. The single case of acute leukemia suggests the point, that in persistent, rapid expulsion of cells, the resultant forms are generally extremely immature, and as would be expected, are of poor resistance.

In these cases the bearing which the degree of leukocyte fragility has on prognosis is not especially striking, but certainly worthy of consideration. To establish the generalizations regarding the estimation of prognosis which are drawn by Mauriac, Carbonat and Moureau on a firm basis, it is necessary to prove the existence of the two major premises on which the generalizations depend. These are (1) that the reaction of living cells to an artificial, unfavorable environment will resemble their reaction to the natural injurious agent of the disease under consideration, (2) that a certain tissue, the leukocytes in this instance, will parallel the resistance of other body tissues perhaps more vitally concerned in the maintenance of the proper functioning of the entire structure. This has not been done in this work. Therefore the conclusions are drawn reservedly on the basis of a certain constancy of results, which suggests the existence, at least in part, of the foregoing premises.

#### SUMMARY

1 A technic has been developed for the determination of the fragility of leukocytes by the microscopic examination of a measured amount of blood, which has been exposed to a hypotonic sodium chlorid, sodium citrate solution for three minutes and then stained with Niagara blue or trypan blue. The technic is believed to be of greater accuracy than the one described by Mauriac, Carbonat and Moureau and to be applicable clinically through its simplicity.

2 Certain influences liable to cause error have been investigated. It has been shown that the hypotonic sodium chlorid, sodium citrate solution must be kept continually on ice to prevent bacterial growth, that the determinations should be done at a constant temperature, preferably about 25 C, and that the solution should be kept in paraffin lined, or hard glass flasks to prevent alteration of hydrogen-ion content. It is appreciated from the protective influences that certain colloids, such as gelatin and Niagara blue, have on the leukocytes in hypotonic solution, that the variable constituency of the blood plasma may possibly play an indeterminate part in some of the results obtained, but it is impossible at present to obtain pure cell suspensions free of plasma without excessive trauma to the cells.

3 An attempt has been made to establish a normal percentage of fragile leukocytes. In fifteen adult males and three adult females under



probable constant conditions, there was a variation of from 43 to 63 per cent of the fragile leukocytes, with 86.6 per cent of the ninety determinations occurring between 45 and 55 per cent

4 In six cases of lobar pneumonia with leukocytosis there was a marked reduction of fragility of the leukocytes in the four patients who recovered, and only a moderate reduction of the fragility in the other cases which terminated fatally

The leukocyte fragility of five cases of pernicious anemia differed very slightly from the normal, except in a single patient shortly preceding death who showed increased fragility

In acute and chronic myelogenous and chronic lymphoid leukemias an increased resistance was noted, except where many immature leukocytes were found in the peripheral blood when the resistance was decreased

Two otherwise dissimilar cases, showing the common finding of severe secondary anemia in a stage of active regeneration, while sending out many young cells, demonstrated an increased resistance

#### CONCLUSIONS

White blood cells recently delivered into the circulation have an increased resistance, excepting presumably, according to the present criteria of morphology, immature cells such as occur in acute leukemia. In patients who succumb to an infection or intoxication, there is evidence that the increased resistance is less marked than in those patients who are holding the infection or intoxication in check or overcoming it

This partially confirms Mauriac's "Oscillation of Defense," which promises to be an additional factor in arriving at a prognosis in at least some of the acute, infectious diseases

# THE INTERPRETATION OF INCREASED BLOOD URIC ACID IN HYPERTENSION

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## REVIEW OF THE LITERATURE

It has been known for over a century that, after nephrectomy, urea accumulates in the blood,<sup>1</sup> and Bright (1834) was aware that this occurs in the disease first described by him. That uric acid may be increased in nephritis was discovered three-quarters of a century ago by Garrod<sup>2</sup> with the aid of his naive string test. Our modern knowledge of the blood chemistry in kidney disease was inaugurated when Strauss<sup>3</sup> demonstrated that the total nonprotein nitrogen of the blood is increased in asthenic uremia, and Widal<sup>4</sup> showed that the blood urea rises in this condition. Successful study of the constituents other than urea which make up the nonprotein nitrogen could only be carried out, after methods for their quantitative determination in small quantities of blood had been developed by Folin and his co-workers. It was then found that uric acid and creatinin also are often increased in renal insufficiency. Myers, Fine and Lough<sup>5</sup> believe that in progressive failure of renal elimination the first of the nitrogenous substances to be retained is uric acid, then urea, and only when the impairment of renal function becomes very marked does creatinin accumulate in the blood. In their opinion, an increase in the uric acid content of the blood in the presence of normal urea and creatinin values is an indication of beginning renal insufficiency, leukemia, gout, etc., of course, being excluded. Kraus<sup>6</sup> also regards the uric acid level of the blood as a fine indicator of retention, resulting from contracted kidneys. This view has found favor with French authors,<sup>7</sup> who speak of "l'uricémie d'alarme" which precedes urea retention.

The occurrence of an isolated uric acid retention as a precursor of the retention of other substances would be of both practical

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\* From the Medical Service of the Montefiore Hospital

1 Prevost and Dumas. *Ann de Chimie et de Physique* **23** 1821

2 Garrod. *Med-Chir Trans* **31** 83, 1848

3 Strauss. *Die chronischen Nierenentzündungen in ihrer Einwirkung auf die Blutflüssigkeit* Hirschwald, Berlin, 1902

4 Widal and Javal. *Compt rend Soc de Biol* **55** 1639, 1903

5 Myers, V. C., Fine, M. S., and Lough, W. G. The Significance of the Uric Acid, Urea and Creatinin of the Blood in Nephritis, *Arch Int Med* **17** 570 (April) 1916

6 Kraus. *Deutsch Arch f klin Med* **138** 340, 1922

7 Jeanbrau, E., Cristol, P., and Nikolitch, S. *J d' Urol* **15** 249 (April) 1923

and theoretical interest, of practical interest because it would furnish a very early warning of impending uremia, and of theoretical interest because it would unequivocally demonstrate that one of the "partial functions" of the kidney (that of uric acid excretion) can be damaged while the others, which are apparently vested in the same cells, remain intact. Quite obviously, a rise in the uric acid level of the blood does not necessarily mean that the ability of the kidneys to excrete this substance has been diminished. Thus the heightened uric acid content of the blood so often seen in leukemia is certainly to be attributed to the increased destruction of nucleoproteins and not to defective elimination. In the same hypertensive subjects who show an increased uric acid content of the blood, hyperglycemia is often to be found, which cannot be due to renal insufficiency, for the urine does not normally contain appreciable quantities of sugar, but must be explained as a derangement of carbohydrate metabolism correlated with the hypertension (hyperadrenalinemia [?], pancreatic arteriosclerosis [?]). Upham and Higley<sup>8</sup> found that in "early chronic interstitial nephritis" the ratio of the amount of uric acid in 100 c c of urine to that in an equal volume of blood is below normal. They state, however, that "in early chronic interstitial nephritis the height of the blood uric acid increase is not a guide to the degree of impairment of the renal concentration power." Hitzengerger and Richter-Quittner<sup>9</sup> studied the purin metabolism in two cases of essential hypertension with a normal blood urea but much increased uric acid in the blood. They found the endogenous factor to be slightly above normal, while any exogenous factor was promptly excreted, thereby demonstrating that the high uric acid content of the blood was not due to impaired excretion of this substance by the kidney.

#### CLINICAL MATERIAL STUDIED

We have studied the uric acid content of the blood in 110 cases of chronic hypertension. All of these cases were of the types ordinarily termed essential hypertension or chronic interstitial nephritis. Each had a diastolic blood pressure of 100 mm of mercury or more. Blood uric acid values of 3.5 mg per hundred cubic centimeters (determined by the method of Folin and Wu) were considered as presenting a hyperuricemia. Of the 110 cases it was found that forty-four, or 39 per cent, had 3.5 mg or more of uric acid per hundred cubic centimeters of blood.

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<sup>8</sup> Upham, Roy, and Higley, H. A. A Study of the Renal Concentration Power for the Uric Acid in Early Chronic Interstitial Nephritis, *Arch Int Med* **24** 557 (Nov.) 1919.

<sup>9</sup> Hitzengerger, K., and Richter-Quittner, M. *Wien Arch f inn Med* **2** 189 (Feb.) 1921.

Eighteen of these forty-three patients also had a blood urea nitrogen of over 20 mg per hundred cubic centimeters. In the remaining twenty-five, constituting 27 per cent of all not showing urea retention, the blood uric acid was 3.5 mg or more per hundred cubic centimeters, while the urea nitrogen was under 20 mg per hundred cubic centimeters. These patients with an increase in uric acid in the absence of urea retention are listed in the table.

These patients all suffered from the so-called essential hypertension, none being admitted to the hospital for any complaint due to renal insufficiency, but for the results of cerebral vascular accidents, myo-

*Patients With Increased Uric Acid*

No	Diagnosis	Blood Pressure	Urea Nitrogen Mg /100 C c	Uric Acid Mg /100 C c	Sugar Mg /100 C c
1	Hypertension, general arteriosclerosis	190/120	18.2	4.5	110
2	Hypertension, cerebral hemorrhage	210/118	11.4	5.1	151
3	Hypertension, pulmonary emphysema	188/105	19.6	4.1	128
4	Hypertension	210/105	19.8	4.2	
5	Hypertension, general arteriosclerosis	190/105	14.4	4.5	118
6	Hypertension, cerebral hemorrhage	260/160	13.4	5.1	103
7	Hypertension, angina pectoris	240/110	9.8	8.1	
8	Hypertension, cerebral hemorrhage	205/130	9.5	4.5	92
9	Hypertension, encephalitis (residual)	210/135	15.1	6.7	113
10	Hypertension, pulmonary emphysema	170/120	17.2	5.0	
11	Hypertension, cerebral hemorrhage, dyspituitarism	225/110	13.7	3.8	122
12	Hypertension terminal cresol poisoning (sulfide)	200/110	12.8	5.5	
13	Hypertension, diabetes mellitus	175/120	16.5	4.4	156
14	Hypertension, cerebral vascular accident	240/130	12.7	3.7	124
15	Hypertension, diabetes mellitus	195/100	15.5	3.5	162
16	Hypertension, cerebral hemorrhage	250/140	15.1	4.0	129
17	Hypertension, diabetes mellitus, gangrene	190/110	8.9	5.5	328
18	Hypertension, chronic cardiovascular disease	176/100	14.6	4.8	121
19	Hypertension, general arteriosclerosis	200/104	19.0	3.5	121
20	Hypertension, diabetes mellitus	240/100	16.4	5.7	350
21	Hypertension, adhesive pleurisy	190/110	18.2	4.6	91
22	Hypertension, mitral stenosis, auricular fibrillation	254/130	15.2	5.2	98
23	Hypertension, myocardial degeneration	152/120	10.9	3.8	154
24	Hypertension, cerebral hemorrhage, myocardial degeneration	200/110	9.8	4.2	91
25	Hypertension, mitral insufficiency	200/105	15.8	5.2	

cardial insufficiency, diabetes, etc. Of the twenty-five patients only one developed uremia. This was Case 24. The patient, about three years after the above blood analysis was made, went into sudden coma which was diagnosed as "acute uremia." Unfortunately the blood chemistry was not studied at this time, so that even in this case it is not certain that the final coma three years later was of uremic nature. The other patients were in the hospital for from periods of a few weeks to over three years after the blood chemistry listed in the table was determined and none of them developed uremia. That the high blood uric acid does not portend nitrogen retention is shown in the following patients of the foregoing series, which were in the hospital for six months or more after the blood analysis listed in the table was made.

## COURSE OF CASES

CASE 2—This patient died two years after the foregoing determinations were made. Shortly before death the blood chemistry was urea nitrogen, 150, uric acid, 35 mg per hundred cubic centimeters.

CASE 6—This patient, after remaining in approximately the same condition for a year and a half, died suddenly of acute cardiac failure with pulmonary edema.

CASE 7—This patient, who had 81 mg of uric acid per hundred cubic centimeters of blood, the highest figure of the cases listed above, was discharged a year later. Though his blood pressure was unchanged, the uric acid had fallen to 45 mg and the blood urea was normal.

CASE 8—This patient was discharged ten months later, with no evidences of nitrogen retention.

CASE 12—This woman, one year after the foregoing chemistry was determined, had a blood urea nitrogen of 112 mg per hundred cubic centimeters. Three years after, when in an unchanged condition, she committed suicide.

CASE 16—This man died ten months later, his blood chemistry shortly before death being urea nitrogen, 210 mg, uric acid, 23 mg per hundred cubic centimeters.

CASE 23—This patient was discharged six months later in an unchanged condition.

CASE 25—This patient was discharged a year later in the same condition.

CASES 1, 2, 10 and 12—These patients came to necropsy. In each case pronounced arteriosclerosis was present, being more marked in the smaller vessels of the kidneys. In each instance a large proportion of the secretory units (glomeruli and tubules) was intact, and apparently amply sufficient to carry on the excretory functions.

## SUMMARY AND CONCLUSIONS

The observations here recorded indicate that these cases of essential hypertension with high blood uric acid, but normal amounts of urea in the blood, show no tendency to subsequent retention of urea and the parallel development of uremia. The patients followed for varying periods, from a few weeks to three years, did not develop renal insufficiency (except in one questionable instance) but suffered from the direct consequences of the circulatory strain, such as myocardial insufficiency or cerebral hemorrhage, or from some complication, most frequently diabetes mellitus. Anatomic investigation of the kidneys of four patients with high blood uric acid, who succumbed to these extra-renal manifestations, did not indicate that renal insufficiency was present. Despite the high content of the blood in uric acid these cases are "benign" so far as the kidney is concerned, and their chief dangers are cardiac failure or cerebral hemorrhage. Observation of the clinical course of these patients shows that the high blood uric acid does not presage impending renal insufficiency. The uric acid content of the blood fluctuates considerably, apart from diet, and apparently has no prognostic significance. We were unable to discern any differences in the symptomatology and course of the cases with hyperuricemia and

those with a normal blood uric acid. Like the hyperglycemia so common in hypertension, the increased uric acid content of the blood is due to metabolic causes and not to beginning renal insufficiency. When renal insufficiency sets in, the uric acid level of the blood rises, but it is then accompanied by a rise in the blood urea, which differentiates the hyperuricemia of renal origin from that accompanying hypertension in the presence of intact kidney function.

# REPORT OF A FATAL CASE OF JUVENILE DIABETIC COMA WITH INSIGNIFICANT KETONURIA, AND WITH A LARGE AMOUNT OF ACETONE IN THE SPINAL FLUID\*

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This fatal case of juvenile diabetic coma is reported because of the presence of several unusual features, namely, (1) the finding of only insignificant ketonuria in spite of extreme acidosis, (2) the presence of a large amount of acetone in the spinal fluid notwithstanding its absence from the blood, and (3) the failure of enormous doses of insulin to influence the blood sugar level

## REPORT OF CASE

The patient, a girl, aged 9 years, Jewish, was admitted in a state of coma to the United Israel Zion Hospital, Jan 7, 1924. The family and past personal history were negative. The patient was in good health until three weeks prior to admission, when she began to suffer from increased frequency and volume of urination, pronounced thirst, itching of the skin and progressive loss of weight. Later she complained of slight disturbance of vision and headache, and two days before entering the hospital there was projectile vomiting not dependent on the taking of food.

*Physical Examination*—The patient lay in profound coma, and the breathing was of the Kussmaul type. The complexion was sallow and cyanosed, and the body showed evidence of recent loss of weight. The breath had a strong acetone odor, the tongue was heavily coated, the gums were inflamed and the teeth showed considerable decay. There were excoriations about the vulva, evidently from scratching. The temperature was 101 F, pulse 130, respiration 42.

The urine had a specific gravity of 1.030, was acid in reaction, and contained 3 per cent of sugar. There was a faint trace of acetone, but no diacetic acid. A second specimen gave the same findings with reference to these ketone bodies.

At the time of admission the blood chemical findings were as follows: Sugar 333, urea nitrogen 30, and creatinin 3.33 mg per hundred cubic centimeters of blood. The carbon dioxide combining power of the plasma as determined by the method of Van Slyke and Cullen was 14.3 per cent by volume.

The patient was treated with lavage of the stomach, forced fluids, and bicarbonate of soda solution by rectal drip and saline infusions. Immediately on admission, 40 units of insulin (H insulin-Lilly) were administered intravenously, followed by a similar dose three hours later, and 30 units after another three hours. Altogether 110 units of insulin were given within twelve hours. In spite of this enormous dosage, there were no twitchings or other evidences of hypoglycemic shock. Neither was there any favorable response to the medication, and death occurred nine hours after the last dose of insulin. At the time of death, blood chemical examination gave the following figures:

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\* From the Pathologic Service, United Israel Zion Hospital, Brooklyn, N Y

Sugar 333, urea nitrogen 75, creatinin 3 and uric acid 18 mg per hundred cubic centimeters of blood. The reaction for acetone was negative. It is noteworthy that 110 units of insulin administered within a period of twelve hours had failed to affect the blood sugar level in the least.

The chemical findings in the spinal fluid drawn immediately after death were as follows: Sugar 300, urea nitrogen 60, creatinin 27 and uric acid 24 mg per hundred cubic centimeters. A surprising finding was the presence of a very large amount of acetone, as judged by the reaction to Legal's test.

#### COMMENT

Severe diabetic acidosis without ketonuria is quite unusual, but authentic cases have been reported. Revillet,<sup>1</sup> in 1914, described a fatal case, clinically one of diabetic coma, in which no acetone was found in the urine and in which Gerhardt's test was negative. Rosenbloom,<sup>2</sup> in 1915, reported three cases of diabetic coma in which the urine showed no trace of acetone, diacetic acid or beta-oxybutyric acid, and contained a normal amount of ammonia nitrogen. McCaskey,<sup>3</sup> in 1916, described a fatal case of diabetic coma in which there was acetone in the urine, but no diacetic or beta-oxybutyric acid at any time. Other cases have been reported.

Starr and Fitz,<sup>4</sup> in 1924, reported a study on 114 samples of urine from eighteen diabetic patients as to their content of acetone bodies and undetermined organic acids, and they found that in about 10 per cent of instances organic acids other than the acetone bodies were present in considerably higher than normal concentration. These authors believe that in certain cases of diabetic acidosis other organic acids than the ketones are encountered, and may play a part in the production of symptoms.

In the present case, the finding of a large amount of acetone in the spinal fluid, notwithstanding its absence from a simultaneous blood specimen, is fraught with possibilities and suggests the desirability of further work along this line.

The failure of large doses of insulin to influence favorably diabetic acidosis is not so unusual as to deserve special comment, but the fact that 110 units of insulin (H insulin-Lilly, which is 40 per cent stronger than the older preparation) administered within twelve hours failed in any way to affect the blood sugar level would appear to be a rare enough finding to be worthy of record.

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1 Revillet. Coma chez une diabétique sans acetonurie, *Lyon med* **122** 815, 1914.

2 Rosenbloom, J. A Form of Diabetic Coma Not Due to the Acetone Bodies, *New York M J* **102** 294, 1915.

3 McCaskey, G W. A Case of Fatal Diabetic Coma Without Diacetic or Beta-Oxybutyric Acid, *J A M A* **66** 350 (Jan 29) 1916.

4 Starr, Paul, and Fitz, Reginald. The Excretion of Organic Acids in the Urine of Patients with Diabetes Mellitus, *Arch Int Med* **33** 97 (Jan) 1924.



## SUMMARY

In the case of a comatose girl, aged 9 years, with the classical symptoms of diabetes mellitus dating back three weeks and with a markedly reduced carbon dioxid combining power of the plasma, the urine revealed only a faint trace of acetone and no diacetic acid. Notwithstanding the fact that there was no acetone in the blood, a very large amount of this substance was found in the spinal fluid. Although 110 units of insulin (H insulin-Lilly) were administered within a period of twelve hours, there was no reaction at all and the blood sugar level was not in the least affected.

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# FATE OF HEXAMETHYLENAMIN IN THE BODY AND ITS BEARING ON SYSTEMIC ANTISEPSIS\*

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## INTRODUCTION

Besides its common use as a urinary antiseptic, hexamethylenamin is alleged to be beneficial, when administered orally and intravenously, in various infectious diseases. Clinically,<sup>1</sup> it has been administered in this way in the treatment of typhoid (Ymaz, Loeper, Ymaz and Ayerza), pneumonia (Loeper, Clarke, Mikhaïloff, Loeper and Grosdidier), nephritis (Loeper and Grosdidier, Loeper, de Matta), epidemic encephalitis (Thomas and Rendu), influenza (Loeper and Grosdidier, Michel), serofibrinous pleurisy (Loeper and Grosdidier, Michel), septicemia (Achard), typhus (Glutard), tuberculosis (Loeper and Wagner), prostatitis and epididymitis (Cooke), bronchitis (Mikhaïloff, Never), and malaria (Plaschkes and Benkovic). A sound basis for the use of hexamethylenamin in various systemic infections appears to be lacking. However, it is conceivable that certain conditions might exist which would permit hexamethylenamin to exert an antiseptic action. These would be concerned with the liberation of formaldehyd in the blood and tissues.

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\* From the Department of Pharmacology, School of Medicine, Stanford University

\* Thesis (Part II) submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy

1 Ymaz. *Semana med* **29** 807-809, 1922. Loeper. *Paris Letter*, J A M A **70** 483, 1918. Ymas and Ayerza. *Prensa Med Argentina*, **5** 215, 1918. Clarke, T W. *Am J Obst* **72** 753, 1915. Loeper and Grosdidier. *Bull et mem soc méd d hôp de Par* **42** 566-569, 1067, 1073, 1918. De Matta. *Amazanos Medical* **1** 81, 1918. Thomas, A, and Rendu, H. *Paris med* **11** 273 (Oct 1) 1921. Michel. *Presse med* **27** 126-127 (March 10) 1919. Loeper and Grosdidier. *Progres méd* **33** 427, 1918. Achard. *Progres méd* **33** 385, 1918. Glutard. *Bull et mem soc méd d hôp d Par* **43** 545, 1919. Loeper and Wagner. *Bull et mem soc med d hôp d Par* **42** 569, 1918. Cooke, E S. *New York M J* **116** 542 (Nov 1) 1922. Neves, A. *Arch de med d enf* **21** 29 (Jan) 1918. Plaschkes and Benkovic. *Wien klin Wchnschr* **29** 1495, 1916. Other references along similar lines but not mentioned in the text are Duthoit. *Antisepsis in Gallbladder*, *Compt rend soc biol* **89** 656, 1923. Von Takats, G. *Arch f klin Chir* **125** 544 (Sept) 1923, and discussions, Davis, E. *Intravenous Injection and Urinary Antisepsis*, *J Urol* **11** 29 (Jan) 1924.

Experimental evidence indicates that hexamethylenamin per se has no antiseptic qualities,<sup>2</sup> and that antiseptics is dependent upon the free formaldehyd liberated by hydrolysis, or decomposition, of hexamethylenamin, which in turn depends on the hydrogen-ion concentration of the medium. Although the degree of decomposition increases with an increase in the hydrogen-ion concentration, it has been reported by Trendelenburg<sup>3</sup> that an appreciable liberation of free formaldehyd occurs on the alkaline side of neutrality. When the drug is taken by mouth it appears that the excretion is incomplete. The incompleteness of excretion might be explained by decomposition of the drug in the body, resulting in the liberation of formaldehyd.

In view of these possibilities and of the favorable clinical reports, the subject was deemed worthy of extended study with the idea of determining, if possible, the rational basis of hexamethylenamin as a systemic antiseptic.

The present investigation, therefore, was planned along several lines: (1) A brief study of the urinary excretion of hexamethylenamin in human subjects was made in order to ascertain the extent of loss of hexamethylenamin in its passage through the body, and also the influence of gastric acidity on this; (2) the extent of hydrolysis of the drug with formaldehyd liberation in solutions and serum mixtures of known chemical reaction, including alkalinity, was ascertained; (3) the extent of decomposition in the blood of animals under conditions most favorable to this, namely, acidosis was tested; and (4) the excretion of formate in the urine of human subjects as an index of the decomposition of the drug over longer periods in the tissues was determined. These features are presented in this order, beginning with the excretory results, since excretion is unavoidably bound up with the fate of the drug in the body.

#### 1 EXCRETION OF HEXAMETHYLENAMIN IN HUMAN SUBJECTS

In some preliminary experiments previously reported by Collins and Hanzlik<sup>4</sup> the quantitative excretion of hexamethylenamin in urine appeared to be quite variable. Falk,<sup>5</sup> who also reported variable excretion, claimed a lower percentage of excretion in nephritic than in normal persons, and made the suggestion that hexamethylenamin might be used as a test of renal functional efficiency. If the drug is partially hydrolyzed in the stomach and tissues, such a test would be of little use.

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<sup>2</sup> Hanzlik, P. J., and Collins, R. J. Hexamethylenamin. The Liberation of Formaldehyd and the Antiseptic Efficiency Under Different Chemical and Biologic Conditions, *Arch Int Med* **12** 578 (Nov.) 1913.

<sup>3</sup> Trendelenburg. *Biochem Ztschr* **95** 146, 1919.

<sup>4</sup> Collins, R. J., and Hanzlik, P. J. *J Biol Chem* **25** 231 (June) 1916.

<sup>5</sup> Falk, K. G., and Sugiura, K. *J Pharmacol & Exper Therap* **8** 39 (Jan.) 1916.

The experiments in this study were made on convalescent patients and healthy subjects. They received doses ranging from 1 to 5.2 gm of hexamethylenamin by mouth. The urines were collected until free from the drug, and then they were subjected to quantitative estimation, by the distillation colorimetric method of Collins and Hanzlik.<sup>4</sup> In some experiments hourly administrations of water and hourly collections of urine were made to determine the influence of diuresis on the excretion. In other experiments, sodium bicarbonate was administered in order to test out the influence of gastric acidity. The results obtained are presented in Table 1.

TABLE 1—*Quantitative Excretion of Hexamethylenamin in the Urine of Human Subjects*

Subject			Quantity of Hexamethylenamin and NaHCO <sub>3</sub> Administered	Per Cent Hexamethylenamin Excreted	Total Volume of Urine Excreted, Cc	Duration of Excretion, Hours	Diagnosis
H W	1 A		Hexamethylenamin 5.2 gm constant H <sub>2</sub> O intake	82.3	1,757	39	Convalescent (acute parotitis)
	1 B		Hexamethylenamin 5.2 gm natural H <sub>2</sub> O intake	40.0	3,485	41	
E L	2 A		Hexamethylenamin 1.0 gm constant H <sub>2</sub> O intake	32	2,470	20	Convalescent (varicella)
	2 B		Hexamethylenamin 1.0 gm natural H <sub>2</sub> O intake	65	1,044	20	
W H	3 A		Hexamethylenamin 1.0 gm constant H <sub>2</sub> O intake	66	1,638	21	Convalescent (measles)
P H	4 A		Hexamethylenamin 1.0 gm	85	2,185	33½	Normal person
	4 B		Hexamethylenamin 1.0 gm and NaHCO <sub>3</sub> 1 gm	100	1,925	24	Normal person
M D	5 A		Hexamethylenamin 1 gm	71	1,905	31½	Normal person
	5 B		Hexamethylenamin 1 gm and NaHCO <sub>3</sub> 5 gm	87	2,053	24	Normal person
P H	4 C		Hexamethylenamin 1 gm and NaHCO <sub>3</sub> 5 gm	86	2,100	24	Normal person
M D	5 C		Hexamethylenamin 1 gm and NaHCO <sub>3</sub> 5 gm	86	2,450		Normal person

Table 1 shows that the total excretion in subjects receiving hexamethylenamin alone was variable, ranging from 32 to 85 per cent. This confirms the results of previous investigators. The excretion lasted from twenty to thirty-three and a half hours with 1 gm doses, and about forty hours with 5.2 gm doses of the drug. The data also show that the total excretion was uninfluenced by diuresis. However, the administration of bicarbonate augmented the excretion. In the four experiments performed on two subjects, excretion before administration of from 1 to 5 gm of bicarbonate was 71 and 85 per cent, after bicarbonate the excretion ranged from 86 to 100 per cent. In other words, neutralization of the hydrochloric acid of the gastric juice tended to increase the excretion of hexamethylenamin in virtue of the decreased hydrolysis of the drug before absorption. The experiments with bicarbonate were not extended further because of difficulties in determining definitely to what extent neutralization of the hydrochloric acid in the

stomach is accomplished. In any case, the median total excretion after bicarbonate in the majority (three) of four experiments still left 14 per cent of the drug unaccounted for, indicating the influence of some other factors. The results obtained indicate that hexamethylenamin administered orally would be unreliable as an agent for testing renal functional efficiency.

Therefore, it is concluded that the urinary excretion of hexamethylenamin is rather variable, leaving from 15 to 68 per cent of the administered drug unaccounted for. The loss is due in part to the destructive influence of gastric acidity, but is independent of the dosage, water intake and diuresis.

Higher doses might be expected to increase the quantity of drug excreted unless decomposition in its passage through the body occurs. This might occur despite the destructive action of the gastric acidity, which, however, is variable. The alkalinity of the intestine would have no part in the destruction. The data in Table 1 show that the total excretion of hexamethylenamin in urine was no greater with doses of 5 and 5.2 gm than with doses of 1 gm. In fact, the higher dosage of 5.2 gm resulted in smaller excretion, namely, from 40 to 86 per cent as compared with a range of from 32 to 100 per cent with 1 gm doses. This suggests the possibility that some other factors besides those of the alimentary tract enter into the decomposition of the drug, namely, the tissues.

## 2 POSSIBLE RÔLE OF THE TISSUES

The rôle of the tissues in the decomposition, or hydrolysis, however small, might nevertheless help to explain the variable excretion, which is characteristic of the drug, and also the beneficial effects of hexamethylenamin administered intravenously, and by mouth, in various infectious diseases. That is, in the hydrolysis or decomposition of hexamethylenamin, liberation of formaldehyd occurs, and in the blood and tissues this product might momentarily exist before oxidation to formic acid. If free formaldehyd could be demonstrated, it would help to reconcile the alleged beneficial effects on a rational basis. On the other hand, if no hydrolysis of hexamethylenamin could be demonstrated under conditions of the blood and tissues, either by the absence of formaldehyd or of ammonia, or products of either of these, then the variability in the total excretion would have to be relegated to variable conditions in the alimentary tract. The same negative results would disprove the alleged beneficial effects of hexamethylenamin intravenously, or by any other channel of administration. Otherwise it would be necessary to postulate some mechanism of antiseptic action other than that generally accepted and there is no justification for this. Therefore, it was decided to determine to what extent, if at all, hexamethylenamin is decomposed under conditions of the blood and tissues.

## 3 HYDROLYSIS OF HEXAMETHYLENAMIN IN BUFFER MIXTURES

In studying the hydrolysis of hexamethylenamin it was thought desirable to secure indirect as well as direct experimental evidence. When the products of hydrolysis, *i. e.*, ammonia and formaldehyd, were determined, the evidence was direct. When estimations of products derived from ammonia and formaldehyd, namely, urea and formic acid, were made, the evidence was indirect. Determinations of ammonia and formaldehyd were feasible in the experiments *in vitro*, but, for reasons that will be indicated later on, the experiments on animals necessitated estimations of urea and formic acid.

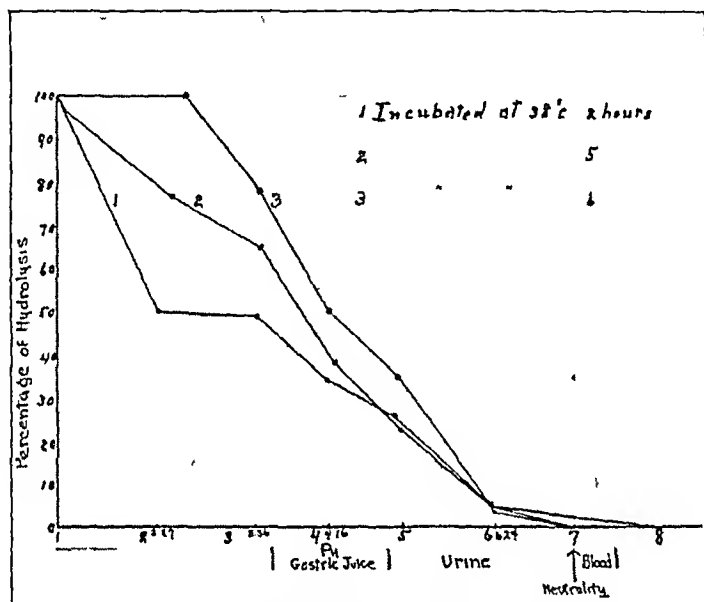


Chart 1—Liberation of formaldehyd from, or hydrolysis of, hexamethylenamin in buffer mixtures, covering ranges of  $p_H$  in gastric juice, urine and blood

Hydrolysis of hexamethylenamin in aqueous solutions of different  $p_H$  values was studied in the following manner. A series of buffer phosphate solutions of known  $p_H$  value for the range of from 5.3 to 8 and of citrate hydrochloric acid for the range of from 1 to 4.9, was placed in volumetric flasks of 100 c.c. capacity, and to each flask was added 0.2 gm. of hexamethylenamin. The mixtures were then incubated at 38°C., and at the end of definite time intervals samples were removed, and estimations of free formaldehyd were made directly by the phloroglucin colorimetric method of Collins and Hanzlik.<sup>4</sup> The results obtained are presented in the form of curves in Chart 1.

These show that the colorimetric method for estimating free formaldehyd was satisfactory for the purpose of this study and that the results (with buffers ranging from a  $p_H$  of 1 to a  $p_H$  of 7) of

Trendelenburg were verified That is, the results indicate a hydrolysis of, with liberation of formaldehyd from, hexamethylenamin more or less proportional to the degree of acidity, being greatest in degrees of acidity higher than and corresponding to that of gastric juice, less in that of urine, and least at neutrality The curves also show a slight amount of hydrolysis on the alkaline side of neutrality, that is, in the range corresponding to and higher than that of blood when incubation was continued for six hours

Since the hydrolysis on the alkaline side is of the greatest interest, the experiment was repeated to obtain more detailed data in the  $p_H$  range of from 6.5 to 8.5, using phosphate mixtures of from 6.5 to 8 and borate hydrochloric acid for the 8.5 mixture The results of this experiment are presented in Chart 2

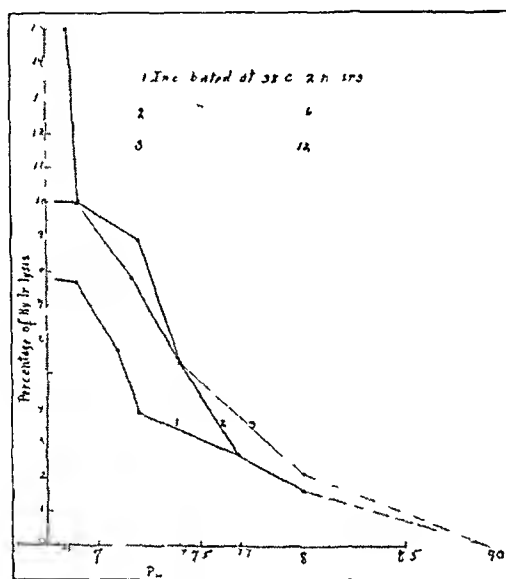


Chart 2—Liberation of formaldehyd from, or hydrolysis of, hexamethylenamin in alkaline buffer mixtures ( $p_H$  range from 6.81 to 9.0)

It is seen that the hydrolysis of hexamethylenamin between  $p_H = 8$  and  $p_H = 7$  ranged from 0.15 to 0.67 per cent after incubating for two hours, from 0.15 to 0.93 per cent after incubation for six hours, and from 0.2 to 0.97 per cent at the end of incubation for twelve hours In this connection the mitigating influence of liberated ammonia was considered because the  $p_H$  values shifted to the alkaline side but was found to be negligible That is, during the hydrolysis of hexamethylenamin there is a liberation of ammonia which might cause a shift of the  $p_H$  value of a given buffer mixture toward the alkaline side and so cause a diminished hydrolysis This factor might be of importance in the  $p_H$  range of from 6.5 to 8.5 To determine the effect of liberated ammonia the  $p_H$  values of the mixtures were deter-

mined by the colorimetric method at the time of analysis for formaldehyd. It was found that the percentage decomposition of hexamethylenamin remained practically the same, and, therefore, the decrease in hydrolysis caused by a shift of the  $p_H$  value to the alkaline side due to the liberated ammonia was negligible.

The results obtained thus far indicate the possibility of formaldehyd liberation from hexamethylenamin in the blood and other body fluids, but the actual demonstration of the formaldehyd in the presence of protein might be different, and, therefore, requires simulation of the conditions in vivo more closely.

#### 4 HYDROLYSIS OF HEXAMETHYLENAMIN IN BUFFER MIXTURES CONTAINING SERUM PROTEIN

Having shown that hydrolysis of hexamethylenamin is a function of the  $p_H$  and that there is an appreciable liberation of formaldehyd at  $p_H$  values greater ( $p_H = 8.0$  and  $7.4$ ) than those of body fluids (blood,

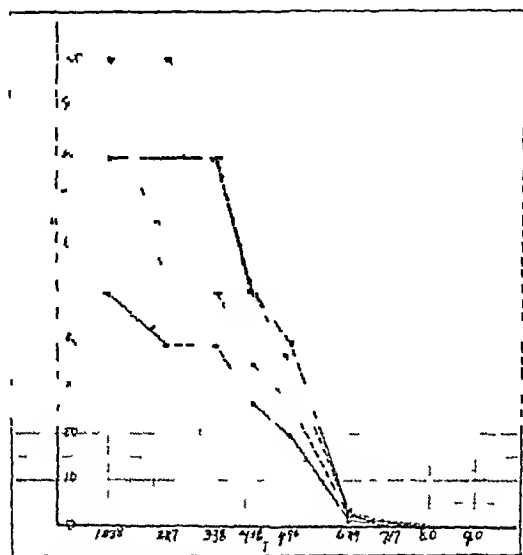


Chart 3—Liberation of formaldehyd from, or hydrolysis of, hexamethylenamin in serum protein. Curves marked 1 indicate incubation for six hours at 38 C, and those marked 2, for two hours at 38 C. Solid lines represent hydrolysis in presence, and broken lines in absence, of horse serum.

cerebrospinal fluid, etc.) the effect of protein on the hydrolysis in the various buffer solutions was studied. The procedure was the same as in the case of buffer mixtures alone except that the buffers contained 5 per cent horse serum. Typical results are presented in the form of curves in Chart 3.

The results obtained show that protein in the form of horse serum had a definite retarding influence on the hydrolysis, or decomposition, of hexamethylenamin at any given  $p_H$  level, and that liberation of formaldehyd was not demonstrable in truly alkaline buffer serum.



mixtures In view of the fact that the phloroglucin reagent is sensitive to formaldehyd in as low a concentration as from one to five million, any undetected formaldehyd in the buffer serum mixtures must have been negligible On the other hand, considerable liberation occurred in the acid mixtures as would be expected, although quantitatively the liberation was less in the presence of serum protein than in the absence of it

## 5 DECOMPOSITION OF HEXAMETHYLENAMIN IN THE CIRCULATION

Although the results with the buffer serum mixtures reduced the possibility of decomposition of, or formaldehyd liberation from, hexamethylenamin in the blood, it still could not be concluded that the drug might not be appreciably decomposed in the circulation and tissues because the conditions in the living organism differ from the experiments in vitro even in the presence of protein Proteins, no doubt, are essential factors in mitigating formaldehyd detection However, this is balanced by several factors, namely, by the hydrolyzing influence of ferments, by the fact that the tissues proper are, in reality, a trifle more acid ( $p_H=6.8$  or thereabouts) than the blood, and by the continuous exposure of hexamethylenamin to the decomposing influences of the tissues These, in virtue of the circulation, are some of the considerations among others less understood, which enter into the possibility that hexamethylenamin may hydrolyze and liberate formaldehyd in the blood tissues In disease conditions, in which the chemical reaction of certain tissues is such as to be favorable to the decomposition, as in the case of pneumonia in which lung extracts were shown to be acid ( $p_H=6.0$ ) by Lord,<sup>6</sup> formaldehyd might be freed, at least momentarily and locally If hydrolysis could be demonstrated in the circulation of normal animals, there would not be much doubt of such hydrolysis (with formaldehyd liberation) in the diseased organs or tissues whose reaction is truly acid, or rendered acid, as by the induction of asphyxia Hence, it was decided to proceed at once to test the proposition, whether or not hexamethylenamin is hydrolyzed in the circulating blood The experiments on animals may now be described

## METHODS

The phloroglucin method, which is satisfactory for the estimation of small quantities of formaldehyd in colorless solutions, cannot be used for either the qualitative detection or quantitative estimation of formaldehyd in a colored medium such as blood Low concentrations

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<sup>6</sup> Lord, F T The Relation of the Pneumococcus to the Production of Acid in Fluid Culture Mediums and the Reaction of the Pneumonic Lung, J A M A 72 1364 (May 10) 1919, 73 636, 786 1364 1420 1919

of formaldehyd in blood cannot be removed quantitatively by dialysis nor by aeration, as shown by the following experiments Formaldehyd in a concentration of from one to five thousand was vigorously aerated with ammonia-free air for three hours, and analysis of the original solution showed that 96 per cent of the formaldehyd had not been removed Aqueous solutions of formaldehyd in concentrations of from one to five hundred thousand were dialyzed for periods ranging from one to twenty hours and the dialyzate never gave more than a faintly positive test for formaldehyd, using the phloroglucin reagent These results are in exact agreement with numerous, unpublished experiments of Hanzlik in which both aeration and dialysis failed to give quantitative removal of formaldehyd from aqueous solutions and from serum

In view of these difficulties, evidence for the presence of formaldehyd in the body fluids after administration of hexamethylenamin had to be obtained indirectly The end products of hexamethylenamin hydrolysis in the organism are sodium formate, and ammonium salts, which are converted to urea Consequently, increases in the blood urea nitrogen, and the presence of formic acid were used as indices of hexamethylenamin hydrolysis in the circulation The urea nitrogen estimations were made by the Van Slyke and Cullen <sup>7</sup> modification of Marshall's method The ammonia was driven over by aeration and estimated colorimetrically in the usual way The formic acid was estimated by a method previously described <sup>8</sup> Briefly, this consists of the removal of interfering substances by picric acid and estimations of the formic acid in the filtrate by causing reduction of mercuric chlorid to calomel, which is then determined volumetrically by means of standard solutions of iodine and of thiosulphate The experiments fell into two main groups (1) urea-nitrogen, and (2) formic acid estimations in the blood

#### CHANGES IN UREA NITROGEN OF THE BLOOD

For a study of these changes experiments were made on rabbits and dogs The results on rabbits will be described first

A sample of control blood was removed by cardiac puncture and the urea nitrogen estimated Then 5 c c of 10 per cent hexamethylenamin was injected into an ear vein, and subsequently samples of heart blood were removed at intervals of fifteen minutes Urea estimations were made immediately after withdrawal of the blood The results obtained on the five rabbits that were used are summarized in Table 2

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<sup>7</sup> Van Slyke, D. D., and Cullen, G. E. A Permanent Preparation of Urease, and Its Use for Rapid and Accurate Determination of Urea, *J. A. M. A.* **62** 1558 (May 16) 1914

<sup>8</sup> De Eds, Floyd. *J. Lab. & Clin. Med.*, 1924 (in press)

It is seen that the results are somewhat variable. They indicate insignificant increases and decreases in the urea nitrogen content of the blood as a result of the injection of hexamethylenamin. Only two rabbits (Nos 3 and 4) showed increases in urea nitrogen, while the other rabbits (Nos 1, 2 and 5) showed corresponding decreases. The decreases in urea nitrogen in Rabbits 1, 2 and 5 might be accounted for by variations accompanying the tendency to the establishment of an equilibrium between the blood and tissues. In the rabbit experiments no allowance was made for possible changes in blood volume. The injection of hypertonic solutions of hexamethylenamin may cause a washing out of urea from the tissues, and so account for the increased urea values shown by Rabbits 3 and 4.

TABLE 2—*Changes in Urea Nitrogen Content of the Blood in Rabbits Produced by Intravenous Injection of Hexamethylenamin*

Rabbit	Dose of Hexamethylenamin Injected, Gm	Mg Urea Nitrogen in 100 Cc of Blood	
		Before Hexamethylenamin	After Hexamethylenamin
1	0.5	10.9	8.7 end of 55 minutes
2	0.5	10.0	9.55 end of 45 minutes
3	0.5	9.5	10.53 end of 15 minutes
			10.26 end of 30 minutes
4	0.5	9.73	10.36 end of 45 minutes
			11.24 end of 15 minutes
			10.75 end of 30 minutes
5	0.5	11.7	10.26 end of 45 minutes
			9.21 end of 15 minutes
			9.30 end of 35 minutes
			9.35 end of 60 minutes
			8.96 end of 105 minutes

More marked increases in urea content of blood might be brought about by inducing asphyxia which lowers the  $p_H$  of the blood, or in other words, causes acidity, and, therefore, should result in increased hydrolysis of hexamethylenamin. Since experiments involving asphyxia over prolonged periods are more suitably and successfully carried out on dogs, the remainder of the experiments were done on these animals.

The dogs received 25 cc of 40 per cent hexamethylenamin intravenously. Blood from the right femoral artery was removed at intervals, and collected under clean liquid petrolatum containing a little dry sodium oxalate for prevention of clotting. Estimations were made of urea nitrogen (by the same method before mentioned), of hemoglobin (by Palmer's method<sup>9</sup>), and of  $p_H$  colorimetrically using phenolsulphonephthalein according to the method of Rowntree, Levy and Marriott,<sup>10</sup> and electrometrically by means of a hydrogen electrode previously described by De Eds and Hanzlik.<sup>11</sup> At the same time kymographic

<sup>9</sup> Palmer J Biol Chem **33** 119 (Jan) 1918

<sup>10</sup> Levy, R. L., Rowntree, L. G., and Marriott, W. McK. A Simple Method for Determining Variations in the Hydrogen-Ion Concentrations of the Blood, Arch Int Med **16** 389 (Sept) 1915

<sup>11</sup> De Eds, Floyd, and Hanzlik, P. J. J Biol Chem **60** 355, 1924

records were made of changes in blood pressure, pulse, and respiration in the usual manner. Toward the end of each experiment, asphyxia was induced by clamping the trachea or attaching to it a long tube in order to increase the dead space. Then blood was drawn and the results of analysis were compared with those of the blood before asphyxia. In order to determine whether or not the changes in urea nitrogen and other constituents of the blood were characteristic for the intravenous injection of hexamethylenamin, control injections of hypertonic (10 per cent) sodium chlorid and 6 per cent acacia were made. The results of the experiments on dogs are summarized in Table 3.

TABLE 3—*Changes in Urea Nitrogen and Other Constituents of the Blood of Dogs Infected Intravenously with Solutions of Hexamethylenamin, and Other Solutions as Controls*

Number and Weight (Kg) of Dog	Doses of Agents Injected	Changes in Blood							Minutes After Injection	Remarks
		$p_{\text{H}}$		Urea Nitrogen Mg per 100 C e		Per Cent Hemoglobin				
		Before Injection	After Injection	Before Injection	After Injection	Before Injection	After Injection			
3 (7.4)	40 per cent hexamethylenamin, 1.3 gm per kg	7.3	7.0 6.6 6.8	10.53	11.49 11.05 11.0	85.1	79.0 75.2 73.0	15 31 54	Asphyxia	
4 (9.88)	4.7 per cent hexamethylenamin, 0.47 gm per kg	7.3	7.3 7.1 7.1 7.0	11.76	13.7	100	96.5 81.0 90.0 98.0	18 60 75 101	Asphyxia	
5 (7.2)	40 per cent hexamethylenamin, 1.36 gm per kg	7.3	7.1 7.2 6.8	8.5	9.76 10.93 11.1	100	92.6 100.0 80.4	24 39 60	Asphyxia	
6 (23.5)	40 per cent hexamethylenamin, 1.7 gm per kg	7.4	7.3 6.0 7.0	13.36	10.0 11.7 11.1	100	100.0	13 21 170		
7 (14.3)	40 per cent hexamethylenamin, 1.4 gm per kg	7.3	7.3 7.4 6.9	8.0	7.5 10.0 8.14	100	93.4 100.0 100.0	17 77 81	Asphyxia	
14 (6.6)	40 per cent hexamethylenamin, 3.0 gm per kg	7.3	7.1 7.0 7.0	15.4	13.8 15.8 14.9	89.7	76.0 73.2 70.7	65 83 113		
16 (5.12)	40 per cent hexamethylenamin, 4 gm per kg	7.0	6.9	14.6	14.6	100	77.5	24		
11 (19)	10 per cent NaCl, 5.2 c c per kg	7.2	7.1	11.3	12.74	100	75.2	23		
19 (13.2)	6 per cent acacia, 16 c c per kg	7.15	7.1 7.0	8.5	9.3 11.1	100	97.0 96.0	31		

The results obtained indicate slight and negligible increases in the urea nitrogen content of the blood in the majority of the experiments, even in those in which asphyxia was induced and when the blood was truly acid, i. e.,  $p_{\text{H}} = 6.8$  to  $6.9$ . In Experiments 1, 2 and 3, increases in urea nitrogen up to 30 per cent occurred, despite dilutions of the blood due to the volume of fluid injected, and to dehydration of the tissues when hypertonic solutions were used. These increases in urea nitrogen may be due to a washing out of urea from the tissues. Since similar increases in nitrogen content of the blood occurred after injection of an isotonic solution (6 per cent acacia in 0.9 per cent sodium chlorid)

and also hypertonic (10 per cent) sodium chlorid solution, the increases cannot be ascribed to hypertonicity, nor to ammonia derived from the hydrolysis of hexamethylenamin

The shifting of the acid base equilibrium in these experiments constitutes a highly important and interesting phase of intravenous injections in general, and will not be discussed here. It has no bearing on the problem at hand.

The chief conclusion to be derived from the experiments on dogs for the purpose of this study is that the results as to the hydrolysis or decomposition of hexamethylenamin as indicated by changes in the urea nitrogen (indirectly ammonia) of blood are negative, even under the most favorable condition of asphyxia (acidity). They confirm the negative results on rabbits, and also those of the experiments in vitro with buffer serum mixtures.

#### CHANGES IN FORMIC ACID CONTENT OF THE BLOOD

Since formic acid is an oxidation product of formaldehyd, it was used as an index of the hydrolysis of hexamethylenamin in the blood.

TABLE 4—*Formate Content of Blood After Intravenous Injection of Sodium Formate in a Dog Weighing 17.5 Kg*

Time	Event	Formic Acid in Blood from	
		Jugular Vein	Femoral Artery
11 10	Blood sample (control)	None	None
11 19	Injection of sodium formate 0.28 gm per kg		
11 25	Blood samples	2.85 mg = 8.2 per cent of injected amount	3.5 mg
12 00	Blood samples	1.7 mg = 0.5 per cent of injected amount	2.25 mg
1 00	Blood samples	0.78 mg = 0.2 per cent of injected amount	0.27 mg

However, before proceeding to the results on formic acid, it should be indicated that the method used could detect formic acid after the injection of formate and of formaldehyd.

The formic acid was determined by the method<sup>8</sup> described in the foregoing. By this method formic acid added to blood in amounts as small as 0.1 mg in 25 c.c. can be satisfactorily determined. As a further check on the method, analyses of the blood were made after injecting 50 c.c. of 10 per cent sodium formate, equivalent to 3.4 gm formic acid, into the femoral vein of a dog weighing 17.5 kg. The blood volume was taken as 9 per cent of the body weight, or about 1,500 c.c., and, therefore, the concentration of formic acid was about 0.23 per cent.

Samples of 15 c c of blood were removed from the jugular vein and femoral artery, the theoretical amounts of formic acid injected being 34.5 mg

The results in Table 4 indicate that the method was satisfactory for determining small quantities of formic acid, such as might be derived from the quantities of hexamethylenamin injected in the experiments to be described. They also show that formate disappears rapidly from the blood stream.

The results in Table 5 obtained on four dogs, injected intravenously with different concentrations of formaldehyd, indicate that detectable quantities of formic acid were found with concentrations of 1/7,000 and over of formaldehyd and that the percentage of formaldehyd oxidized to formic acid increased up to two hours. We may now briefly summarize the results of the experiments with hexamethylenamin.

TABLE 5—*Percentage Conversion of Formaldehyd to Formic Acid in the Circulation of Dogs*

Dog	Weight, Kg	Concentration of Formaldehyd Injected into Blood Stream	Per Cent Converted to Formic Acid	Remarks
1	14	1/2,500	3.9 at end of 25 minutes 8.8 at end of 1 hour	Blood from heart
2	8.6	1/5,000	5.8 at end of 13 minutes 16.0 at end of 35 minutes 20.0 at end of 65 minutes	Blood from heart
3	9.5	1/7,000	1.6 at end of 2 hours and 15 minutes None at end of 2 hours and 40 minutes	Blood from jugular vein
4	8.6	1/15,000	None	Blood from femoral artery

Three dogs (Experiments 7, 9 and 10) were injected with a 10 per cent solution of hexamethylenamin into the femoral vein after removal of control samples of blood. Then three samples were removed at approximately 30 minute intervals, and finally two samples in each case were taken after inducing asphyxia for the purpose of procuring the conditions most favorable for the liberation of formaldehyd. Electrometric and colorimetric determinations of the  $p_H$  of asphyxial bloods showed definite acidity in each case ( $p_H = 6.81$  to  $6.9$ ). However no formic acid was demonstrable in the bloods of all dogs before and after asphyxia. These negative results agreed with the relatively low, or almost negligible, hydrolysis of hexamethylenamin in vitro in the presence of 5 per cent horse serum, which did not exceed 0.1 per cent (Chart 3). The average blood volume of the dogs receiving injections of the drug was 900 c c and the amount of drug injected was 25 c c of a 10 per cent solution, or 2.5 gm. If only 0.1 per cent were hydrolyzed, the concentration of liberated formaldehyd would be about

1 300,000, providing the formaldehyd so liberated had been retained in the circulation. This is below (about one-tenth) the concentration of formaldehyd necessary for antiseptics. It is also probably smaller than the concentration of formaldehyd necessary for liberation of demonstrable formic acid in the blood. In other words, the results of the experiments on dogs and on hydrolysis *in vitro* are in essential agreement. They indicate that hydrolysis of hexamethylenamin in the blood is negligible and, therefore, that the concentration of liberated formaldehyd would be too small to be efficacious as an antiseptic.

## 6 EXCRETION OF FORMIC ACID IN URINE

The possibility still remains that formic acid might be formed slowly and appear in the circulation in amounts too small to permit estimation by the method used for blood. This might occur from slow decomposition of the hexamethylenamin itself, or of some combination of the liberated formaldehyd with or in the tissues, the combined formaldehyd requiring more time for oxidation to formic acid than was allowed in the acute experiments on animals. On the other hand, the absence of formate in hexamethylenamin urine collected until the excretion was completed (i. e., for from 2 to 3 days) would practically dispose of the occurrence of formaldehyd in the tissues, whether free as an intermediary product before conversion to formic acid or in some other oxidizable form. Combined formaldehyd in the blood and tissues would be of no more value as an antiseptic than hexamethylenamin itself. The matter was put to a test.

Determinations were made of the total excreted formate in three subjects, one of whom was a febrile patient, and two were healthy. The method used for estimation of formic acid in urine has been described in the foregoing.<sup>8</sup> Hexamethylenamin in doses varying from 1 to 5 gm. was administered by mouth, and total collections of urine (preserved with chloroform) made from the normal subjects, that is, until completion of the excretion of the hexamethylenamin and formaldehyd, as indicated by negative bromin water and phloroglucin tests, respectively. The excretions lasted for one and two days in the two healthy subjects. Only a partial collection of urine (during the first thirty-six hours after administration of hexamethylenamin) was made from the febrile patient. The formic acid was then estimated in aliquot portions of all the urines. The results that were obtained are briefly summarized in Table 6.

It is seen that the two healthy subjects excreted demonstrable though relatively small quantities of formic acid, amounting to 0.31 and 0.26 per cent. of the total hexamethylenamin administered. Subject 1 (F. D.), receiving the higher dose, excreted a greater absolute quantity and higher percentage of formic acid than Subject 2 (M. L. T.) who

received less than one-half the dose. The excretion, therefore, appeared to be influenced by the dosage, the absolute quantity of formic acid excreted being roughly proportional to the dosage. However the excretion was independent of the diuresis, i. e., the total volume of urine excreted, since Subject 1 who excreted more formic acid had a smaller output of urine than Subject 2, whose output of urine was greater and excretion of formic acid smaller. The febrile patient excreted no demonstrable formic acid during the first thirty-six hours after administration of the drug, and despite a collection of 3,000 cc of urine, the highest output of all the subjects. The dosage of the drug also was the highest. Although the collection of urine from the patient was not complete, it extended over a considerable period (thirty-six hours) and formic acid was expected, but not found. During similar periods, formic acid was found in the urines of the

TABLE 6—*Excretion of Formic Acid in Urine of Human Subjects Receiving Hexamethylenamin*

Subject	Body Weight, Kg	Dose of Hexamethylenamin Administered, Gm	Total Volume of Urine, Cc	Total Formic Acid Excreted, Gm	Per Cent Formic Acid Excretion of Total Hexamethylenamin Administered
1 (F. D.) (healthy)	55	2.5	1,500	0.0154	0.31
2 (M. L. T.) (healthy)	77	1.0	1,750	0.0050	0.26
3 (H.) (febrile) (103 F°)	90	5.0	3,000	None	None

two healthy subjects. The sensitivity of the method used for estimation of the formic acid was great enough, namely, 1:150,000, leaving no doubt that the urine was practically formic acid free. Hence, it appears that there was a complete oxidation of the formaldehyd or formic acid (to carbon dioxide and water) in this patient, as might occur from the high fever which was present. If this is true, antiseptic action from formaldehyd in infectious diseases (febrile usually) would hardly be expected. The time at disposal did not permit the study of other febrile patients. The results on the healthy subjects, in whom very little formic acid was liberated, indicated that excretion required no further study for the purpose of this investigation.

It was estimated from the results on Subject 1, in whom the greatest decomposition of hexamethylenamin occurred, that the concentration of formaldehyd in the blood could not have exceeded 1:500,000, and in Subject 2, not over 1:2,000,000. These figures were arrived at by assuming the blood volume to be about 9 per cent of the body weight and the existence of all the formaldehyd (precursor of the formic acid) at one time. However, this probably was not the case, because the excretion lasted for one and two days, and, therefore, at any given



moment the concentration of formaldehyd in the blood was much less. Hence, it is clear that antiseptic qualities could not be conferred on the blood and tissues.

It is concluded that the administration of relatively small doses (1 and 2.5 gm) of hexamethylenamin to healthy human subjects results in the excretion of small quantities (0.005 and 0.0154 gm) of formic acid (as formate) in urine, amounting to about from 0.26 to 0.31 per cent of the total drug administered, and indicating that the liberation of formaldehyd, as precursor of formic acid, in the tissues is too small for systemic antiseptics. In fever, formic acid may not be demonstrable, suggesting complete oxidation of the formaldehyd or formic acid, this condition, therefore, not favoring antiseptics.

#### COMMENT

The results have been sufficiently discussed throughout the text and need no further discussion here, except to indicate briefly their bearing on systemic antiseptics from hexamethylenamin. Studies of the urinary excretion showed that from 15 to 68 per cent of the drug remained unaccounted for, indicating a marked loss of the drug in its passage through the body and agreeing with reports of other investigators. A part of this loss was accounted for by hydrolysis or decomposition of the drug in the alimentary tract (chiefly in the stomach). It appeared that decomposition in the tissues might account for the remainder. Tests of this were made, using direct and indirect evidence *in vitro* and *in vivo*. It was found that slight liberation of formaldehyd from the drug occurred in alkaline serum protein mixtures *in vitro*, the liberation being considerable in acid mixtures as would be expected. However, when blood was rendered definitely acid by asphyxia in animals (until death) injected with large doses of the drug, no increases in the production of decomposition or hydrolysis (ammonia, indicated by urea nitrogen, and formic acid) of hexamethylenamin were demonstrable. Small quantities of one of these products, namely, formic acid, were demonstrable in the urine of two healthy subjects receiving small doses of hexamethylenamin. This was probably due to the longer time allowed for collection of the formate in the excretion experiments than was allowed in the acute experiments on animals, in whose bloods the concentrations of the formic acid probably were too low for estimation. It appears therefore, that formaldehyd, as precursor of formic acid, is liberated in the tissues. However, the concentration at any given moment is much too low for antiseptics, amounting to about 1:500,000 at best, in a subject receiving 2.5 gm of hexamethylenamin, or in other words, about one-twentieth of the concentration (1:25,000 or thereabouts) necessary for antiseptics. With higher doses the concentration might be higher, but at any given moment

and during the time of liberation the concentration would be much less than the highest estimated from the results in this paper. From all this, it follows that the alleged beneficial effects from hexamethylenamin systemically in various infectious diseases cannot be explained on the presence of adequate liberation of formaldehyd in the circulation and tissues. The drug itself is not antiseptic.

Taking the results of this study as a whole, two deductions appear justified. First, the incomplete and variable urinary excretion of hexamethylenamin, after administration by mouth, is accounted for by loss of the drug, that is, by hydrolysis or decomposition, in the alimentary tract, largely in virtue of gastric acidity, which is variable. The formaldehyd liberated in the stomach is not absorbed, as is well known. The decomposition of the drug in the tissues, as indicated by the excretion of formic acid, is very small, and accounts for only a very small fraction of the loss. Secondly, there is no good basis for the use of hexamethylenamin, orally or intravenously, as a systemic antiseptic in various infectious diseases and localized infections. Here again the excreted formic acid is too small in amount to account for the alleged benefits on the basis of the very low concentration of formaldehyd that might be liberated as an intermediary product to or precursor of the formic acid.

### CONCLUSIONS

1 The total urinary excretion of hexamethylenamin administered to human subjects, in doses ranging from 1 to 5 gm, was found to be rather variable, ranging from 32 to 85 per cent, independently of dosage of the drug, diuresis and clinical condition.

2 Oral administration of sodium bicarbonate increased the excretion in two subjects (up to 100 per cent in one), indicating that hydrolysis or decomposition of the drug occurs in the alimentary tract, chiefly in virtue of gastric acidity. In other tests, the excretion was virtually unchanged, indicating partial decomposition of hexamethylenamin by the tissues.

3 Decomposition, as indicated by liberation of free formaldehyd, in buffer phosphate mixtures *in vitro* was found to be a function of the hydrogen-ion concentration, that is, it increased with increases in true acidity. An appreciable liberation of formaldehyd was demonstrable on the alkaline side of neutrality.

4 In buffer mixtures containing serum protein the decomposition was much less as would be expected. At a  $p_H$  of 6.8 the maximum decomposition was about 0.1 per cent, and traces of formaldehyd were demonstrable at a  $p_H$  of 7.2 (vicinity of blood reaction).

5 In acute experiments intravenous injections of large doses of hexamethylenamin in animals did not yield evidence of decomposition as indicated by changes in or presence of decomposition products of the drug, namely, changes in ureanitrogen from the ammonia, and of formic acid (the oxidation product of formaldehyd) even under the most favorable conditions, that is, acidity ( $p_H$  6.8) of blood induced by asphyxia

6 Excretion experiments over longer periods in two healthy human subjects, receiving 1 and 2.5 gm of hexamethylenamin orally, indicated that 0.26 and 0.31 per cent respectively, of the drug were converted to formic acid in its passage through the body. In a febrile patient receiving a higher dose than the healthy subjects, namely 5 gm of the drug, no formic acid appeared in the urine

7 This means that either no formaldehyd (as precursor of formic acid) or only traces were liberated from hexamethylenamin in its passage through the blood and tissues

8 Therefore, from all this, it appears that the hexamethylenamin (when given by mouth) unaccounted for by urinary excretion is lost or decomposed in the alimentary tract, chiefly in virtue of gastric acidity, and that there is no rational basis for the use of the drug, orally or intravenously, as a systemic antiseptic in the treatment of various infectious diseases and localized infections

# THE EFFECTS OF MITRAL STENOSIS, PULMONIC STENOSIS, AORTIC REGURGITATION AND HYPERTENSION ON THE ELECTROCARDIOGRAM\*

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Just seven years ago Dr Arlie V Bock and I<sup>1</sup> presented before the American Society of Clinical Investigation a report entitled "Electrocardiographic Evidence of Abnormal Ventricular Preponderance and of Auricular Hypertrophy" That report was based on the electrocardiograms of about 1,000 cases studied in the course of two and one-half years at the Massachusetts General Hospital Our conclusions were that mitral stenosis and pulmonic stenosis do often affect the electrocardiogram to produce an abnormal swing of the electrical axis of the heart to the right, and that hypertension and aortic regurgitation often cause an abnormal swing of the axis to the left We used the formula which Lewis<sup>2</sup> had suggested in 1914, simply the sum in tenths of a millivolt of the amplitudes of R in Lead I plus S in Lead III minus the sum of S in Lead I plus R in Lead III, that is  $(R_1 + S_3) - (S_1 + R_3) = \text{index}$  A value of this index more positive than + 20 we considered generally abnormal left axis deviation, and more negative than -15 generally abnormal right axis deviation We had on our list eighty-two cases of the former and twenty-two of the latter As the result of constant observations in the last seven years we have made but one change in this regard We now feel that -10 rather than -15 should be the borderline of normal with respect to right axis deviation

Shortly after the war, Carter, Richter and Greene<sup>3</sup> published the description of a method for determining the electrical axis of the heart by using Einthoven's equilateral triangle and measuring by angle, the right horizontal radius of the circle surrounding the triangle being the zero degree line Radii above this give negative values and below positive The normal limits we have taken at 0 and + 90 degrees, that

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\* From the Massachusetts General Hospital

\* Read before the Association of American Physicians, Atlantic City, N J, May 6, 1924

1 White, P D, and Bock, A V Am J M Sc **156** 17 (July) 1918

2 Lewis, T Heart **5** 398, 1914

3 Carter, E P, Richter, C P, and Greene, C H Bull Johns Hopkins Hosp **30** 162 (June) 1919

is, any angle falling in the right lower quadrant of the circle. We have used this method as well as the formula described previously in the analysis of all our cases. Usually, the two methods are in agreement but often they are not. Neither one is wholly reliable. Both are quite arbitrary but both seem to work out clinically fairly equally. In the case of significant right axis deviation, the angle method is in general perhaps more satisfactory than the index, while in the case of left axis deviation the index seems to fit better. We make a routine practice now of using both methods to measure abnormal axis deviation.

A few years ago Herrmann and Wilson<sup>4</sup> showed that there is little agreement between these methods of determining axis deviation and actual ventricular weights as determined at necropsy. Clinically, however, the influence of uncomplicated mitral stenosis, stenosis, hypertension, and aortic regurgitation on the electrocardiogram is a clear one. There are certain reasons for the discrepancies between the

TABLE 1—*Cases with Electrocardiograms Showing Abnormal and Normal Electrical Axis Deviation*

Number of cases	Right	Left	None
	288	398	100
	Per Cent	Per Cent	Per Cent
Mitral stenosis *	53	3(—)	14
Pulmonary stenosis *	7	0	0
Congenital dextrocardia *	2	0	0
Hypertension *	3(—)	30	3
Aortic regurgitation *	1(—)	20	4
Aortic stenosis *	0	2	0
Combined lesions and miscellaneous	34	45	79

\* Uncomplicated

electrocardiograms and actual ventricular weights. In the first place, as Burwell and I<sup>5</sup> pointed out a few years ago, the electrocardiogram at best is a crude measurement in this respect, as accurate as it may be in other regards. It is an arbitrary record made from three lead points in one plane, while of course the heart is a solid body and has three dimensions. Secondly, the shape of the person alters the anatomic axis considerably and also the electrical axis of the heart, and, of course, the actual ventricular weights do not take this into consideration.

Also it is quite probable that dilatation as well as hypertrophy plays its part in altering the electrocardiogram. Slight changes in intraventricular conduction rates undoubtedly play their part too. And finally it is probable, as has been already suggested, that there is an individual variation in the architecture of the auriculoventricular conduction tissue in different people. However these various factors may play their

4 Herrmann, G. R., and Wilson, F. N. *Heart* 9:91 (April) 1922.

5 White, P. D., and Burwell, C. S. *Tr. Am. Soc. Clin. Investigation*, 1921, p. 20.

part, we do know that there is often significance clinically in electrocardiographic variations pointing to abnormal right or left axis deviation, as the following data will show. Cases showing intraventricular block are not included in this study.

In the course of nine years, over 4,000 persons, mostly cardiac patients, have been electrocardiographed at the Massachusetts General Hospital. Of these, 288 showed abnormal right axis deviation by either of the two methods I have described above. Fifty-three per cent of these 288 cases had mitral stenosis, 7 per cent had pulmonary stenosis and 2 per cent had congenital dextrocardia, a total of 62 per cent. This may be compared with 100 unselected cases showing no abnormal axis deviation by either method, with 14 per cent mitral stenosis and no cases of pulmonary stenosis or congenital dextrocardia.

During this interval of time there were 398 cases showing abnormal left axis deviation by either or both methods. Of these, 30 per cent had hypertension of 170 mm of mercury or over (systolic), 20 per cent had aortic regurgitation, and 2 per cent had aortic stenosis without

TABLE 2—*Relationship of Clinical Diagnosis to Electrical Axis Deviation*

Total number cases	Normal	Mitral Stenosis*	Pulmonary Stenosis*	Hypertension*	Aortic Regurgitation*
	100 Per Cent	100 Per Cent	20 Per Cent	100 Per Cent	50 Per Cent
Abnormal right axis deviation	8	47	100	2	4
Abnormal left axis deviation	11	7	0	55	50
Normal axis deviation	81	46	0	43	46

\* Uncomplicated

obvious regurgitation, a total of 52 per cent. In the unselected group of 100 cases showing no abnormal axis deviation, there were only three cases with hypertension, four with aortic regurgitation, and none with aortic stenosis, a total of 7 per cent.

We have also made a study of the subject from the standpoint of clinical diagnosis. One hundred normal people of both sexes, and ranging in age from 8 months to 83 years, showed 8 per cent with an index more minus than  $-10$ , which 8 per cent included the only two people who gave an angle greater than  $+90$  degrees. Three per cent of these 100 normal persons showed an index greater than  $+20$ . Two of these three cases had an angle of less than 0 degrees and there were eight additional persons with normal index but angle in the right upper quadrant.

#### COMMENT

For comparison, 100 cases of mitral stenosis uncomplicated by aortic regurgitation or hypertension were studied, 43 per cent showed an index more negative than  $-10$  and an additional 8 per cent had an index of just  $-10$ . Not one of the 100 cases had an index as high

as  $+20$  Thirty-seven per cent showed an angle greater than  $+90$  degrees, thirty-three of whom are already included in the forty-three showing an index more negative than  $-10$  Nine cases gave an angle of just 90 degrees Seven cases showed a negative angle

Incidentally, of the 57 cases showing normal rhythm of these 100 cases of mitral stenosis, forty-four (or 77 per cent) had abnormally high P waves in Lead I (over one millimeter high), Lead II (over two millimeters high) or in both leads

Twenty unselected cases of probable pulmonary stenosis in congenital heart disease all showed an index more minus than  $-10$  and all but three had angles greater than  $+90$  degrees, these three exceptions having angles of just 90 degrees Incidentally in every case the P wave was abnormally prominent in Lead I (over one millimeter high), Lead II (over two millimeters high), or in both leads, indicating auricular hypertrophy, a fact not hitherto recorded so far as we know

One hundred unselected cases of uncomplicated hypertension showed an index of over  $+20$  in 44 per cent and a negative angle in 47 per cent, as compared with 3 per cent and 10 per cent, respectively, in the group of 100 normal persons Only two of the hypertensive cases gave an index more minus than  $-10$  and none had an angle as great as  $+90$  degrees

Finally fifty unselected cases of aortic regurgitation uncomplicated by mitral stenosis or hypertension were studied, 38 per cent of them showing an index of over  $+20$  and 40 per cent, a negative angle But two cases had an index more minus than  $-10$  or an angle over  $+90$  degrees

#### SUMMARY

Thus, in summarizing, it is evident that there is a definite relationship between abnormal right axis deviation by electrocardiogram and mitral stenosis and pulmonic stenosis, and between abnormal left axis deviation and aortic regurgitation and hypertension Also the auricular complex of the electrocardiogram in Lead I, Lead II, or both, is almost always abnormally prominent in cases of pulmonary stenosis and of mitral stenosis

# A NEW LIVER FUNCTION TEST

THE ELIMINATION OF ROSE BENGAL WHEN INJECTED INTO THE  
CIRCULATION OF HUMAN SUBJECTS <sup>†</sup>

G D DELPRAT, M D , N N EPSTEIN, M D

AND

WILLIAM J KERR, M D

SAN FRANCISCO

Various tests, which have been devised to estimate the functional capacity of the liver, have not proved to be of great clinical value. Most of these tests have been used in an attempt to study only one of the several well known functions of the liver. More recently some of the dyes have been employed as permeability tests for liver activity. Among the dyes advocated for this purpose have been methylene blue,<sup>1</sup> congo red,<sup>2</sup> indigo carmine,<sup>3</sup> and phenoltetrachlorphthalein. The last of these dyes has been most extensively studied. Rowntree, Hurwitz and Bloomfield<sup>4</sup> tried to estimate the permeability of the liver by the extraction of the dye from the feces after injection into the blood stream. This method was subject to many sources of error in the collection and extraction of feces and its use has largely been abandoned. The next step in advance was the modification of McNeil,<sup>5</sup> who used the duodenal tube and determined the amount of dye recoverable from the intestine. This method had obvious clinical limitations because of the difficulties in passing the duodenal tube and in collecting all the bile secreted in a given time. The test was further modified by Piersol and Bockus,<sup>6</sup> who probably achieved greater accuracy in estimating the appearance time of the dye in the duodenum after intravenous injection.

An approach to the problem from a different angle was made by Rosenthal<sup>7</sup> who devised a method of investigating the liver by inject-

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<sup>†</sup> From the Department of Medicine, University of California Medical School

<sup>†</sup> Read before the Southern California Medical Association, Santa Barbara, Calif, April, 1924

1 Cohn, H M. *Klin Wchnschr* **1** 2522 (Dec 16) 1922

2 Lepehne. *Munchen med Wchnschr* **69** 342 (March 10) 1922

3 Einhorn, M, and Laporte, G L. *New York M J* **118** 350 (Sept 19) 1923

4 Rowntree, L G, Hurwitz, S H, and Bloomfield, A L. *Bull Johns Hopkins Hosp* **24** 327, 1913

5 McNeil, H L. *J Lab & Clin Med* **1** 822, 1915

6 Piersol, G M, and Bockus, H L. Observations on the Value of Phenoltetrachlorphthalein in Estimating Liver Function, *Arch Int Med* **31** 623 (May) 1923

7 Rosenthal, S M. *J Pharmacol & Exper Therap* **19** 385 (June) 1922, A New Method of Testing Liver Function with Phenoltetrachlorphthalein, *J A M A* **79** 2151 (Dec 23) 1922



ing the dye into the blood stream and observing the concentration of the dye remaining after certain intervals of time Rosenfield and Schneiders<sup>8</sup> have used an almost identical method, with some variations in technic The results obtained by the latter two investigators, Rosenthal<sup>7</sup> and Rosenfield and Schneiders,<sup>8</sup> are in direct accord with our findings with rose bengal, since they show that phenoltetrachlorophthalein and rose bengal remain in the circulation for a longer period of time in cases where there is evidence of liver disease This retardation in the elimination has been taken as evidence of liver injury

In a previous communication one of us<sup>9</sup> discussed the elimination of rose bengal from the circulation after its injection into the blood stream of dogs, and the variation of the rate of its elimination after experimentally produced liver injury In this paper we will point out the close similarity between the rate of elimination of the dye after injection into the human circulation and its elimination after injection into the circulation of dogs, and will note the modification of this rate of elimination in cases of definite liver disease

#### METHOD

The dye used in these experiments, as before mentioned, is rose bengal, diiodotetrachlorfluorescence of the triphenylmethane series As stated in our previous paper it was found to be entirely eliminated by the liver after injection into the circulation, the urine remaining free from the dye in animals No evidence of toxicity was noted from dosages up to 100 mg of the dye for a dog weighing 18 kg We felt encouraged to try the same method on human subjects, using smaller doses We found, however, in one subject that the dye caused a rise in temperature, in another a rise in temperature and a slight chill occurred The latter (Case 16) had a marked, and the former, a moderate retention of the dye in the blood stream In all cases, including those with marked biliary obstruction, the urine remained free from the dye, with the exception of Case 14, in which a most marked retention of the dye in the blood stream was observed This patient suffered from carcinoma of the common bile duct It is of interest to note that the ascitic fluid of Case 21, withdrawn soon after the injection of rose bengal into the blood stream, showed traces of the dye, but they were too small to estimate Further work on the physiologic chemistry and the extremely interesting behavior of the

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8 Rosenfield, H H, and Schneiders, E F Improved Phenoltetrachlorophthalein Test for Liver Function, *J A M A* 80 743 (March 17) 1923

9 Delprat, G D, Jr Studies on Liver Function, Rose Bengal Elimination from the Blood, as Influenced by Liver Injury, *Arch Int Med* 32 401 (Sept) 1923

dye has been undertaken by Dr C L A Schmidt in the Department of Biochemistry, University of California Medical School

Another characteristic of the dye is its photodynamic activity which, as has been demonstrated by Schmidt and Norman,<sup>10</sup> is more marked in rose bengal than in the other members of the triphenylmethane series. This property of the dye is of practical moment in its application in this work since in our earlier human subjects we experienced considerable difficulty with hemolysis. To reduce this factor to a minimum the technic of the test has been modified in that the blood is collected and kept before centrifugating in a subdued light and centrifugated as soon as possible after collection. As a precautionary measure the patient is kept in a darkened room for an hour following the injection of the dye although it is improbable that sunlight would have a markedly deleterious effect on a patient into whom the dye had been injected, since the injection of 100 mg into a normal dog weighing 9 kg caused no discernible effect after the dog had been exposed to sunlight for several days. This point was not emphasized in our previous paper, because the red cells of the dog appear to be more resistant to hemolysis than human red cells.

The technic described further on seems to have certain advantages in the first place the patient is subjected to a single puncture of the vein, secondly, the actual time of operation on the patient is less than ten minutes and the final mathematical result of the test is available in sixty minutes from the time of its commencement. The dye is easy to obtain in bulk, can be sterilized without chemical change and is not expensive.

#### TECHNIC

The technic of injection of the dye and the collection of blood samples is exactly the same as that described in our previous paper. A vein in the cubital fossa is selected and a sample of blood is withdrawn with a syringe and discharged into a graduated centrifuge tube containing 2 c c of a 2 per cent solution of potassium oxalate. Without the needle being removed from the vein, either 100 or 150 mg of the dye, in a sterile 1 per cent physiologic sodium chlorid solution, is injected and the needle washed out by a further injection of 5 or 10 c c of the solution. The needle is left in the vein, and at exactly two minutes after the injection of the dye a sample of blood (10 c c) is withdrawn from the needle still in situ into a fresh syringe, and discharged into another graduated centrifuge tube containing 2 c c of oxalate solution. The needle is again washed by injecting 5 or 10 c c of physiologic

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<sup>10</sup> Schmidt, C L A, and Norman, G F. Protection Afforded to Red Cells Against Hemolysis by Eosin, *Jour Infect Dis* 27 40 (July) 1920, *J General Physiol* 6 681 (July) 1922

sodium chlorid solution, which maneuver prevents the clotting of blood in the needle. At four and eight minutes, respectively, from the time of injection samples of blood are withdrawn and collected in an identical manner. The needle is then withdrawn from the vein in the arm and the patient is told to remain in the darkened room for an hour. It is our practice to advise the patient that the appearance of the dye in the stools will impart to them a distinct red color, since the unexpected appearance of the red stools may cause considerable alarm.

As soon as possible after collection, the blood samples are centrifugated at a speed of 2,000 revolutions per minute for thirty minutes. The percentage of cells and plasma in each tube is then carefully noted. Three cubic centimeters of plasma from the samples of blood taken at two, four and eight minutes respectively after the time of injection, are then diluted in separate tubes with an equal volume of physiologic sodium chlorid solution, and the color of the dye in these solutions is compared in a Helling colorimeter, with a standard solution containing 5 c.c. of plasma from the "control tube," that is, the sample of blood withdrawn from the vein before the injection of the dye, and 5 c.c. of an 0.0075 per cent solution of rose bengal. It is evident that an allowance must be made for the fact that the plasma in the graduated centrifuge tube contains 2 c.c. of potassium oxalate solution, and that some correction of the colorimeter reading must be made to allow for this dilution.<sup>11</sup>

11 For example, after centrifugating for thirty minutes the graduated centrifuge tube contained 43 c.c. of cells and 70 c.c. of supernatant fluid. The colorimeter reading of the plasma was 25 per cent of the standard (0.0075 per cent solution). If this plasma did not contain the 2 c.c. of oxalate the reading would have been twenty-five times 70 divided by 50. But the dye which is found in the supernatant 50 c.c. of plasma was, before centrifugating in the total 93 c.c. of blood. Hence the correction of the colorimeter reading, giving the correct percentage of the dye in the blood stream, is represented by  $\frac{25 \times 70 \times 50}{50 \times 93}$  (which is 188) per cent of the 0.0075 per cent solution of rose bengal. After these corrections have been made we obtain what we have termed "corrected colorimeter readings," such as are found in the charts.

Having obtained the concentration of the dye in the blood sample withdrawn two minutes after the injection of the dye and knowing the total amount of the dye injected into the circulation, it is a matter of simple proportion to calculate the blood volume of the person.

To continue the given example, two minutes after injection of 100 mg. of dye into the circulation the concentration of the dye in the blood was 188 per cent of an 0.0075 per cent solution of the dye, which is 0.00141 per cent. That is, 100 c.c. of blood contains 1.41 mg. of dye. Therefore, the blood volume of the person, into which this injection was made is  $\frac{100 \times 100}{1.41}$  c.c., or 7,092 c.c.

This can readily be reduced for convenience in calculation to the following formula, which differs somewhat from the formula of our previous paper:

$$\text{Blood volume} = \frac{\text{Milligrams of dye injected} \times \text{volume of blood withdrawn} \times 10^9}{\text{Uncorrected colorimeter reading} \times 0.0075 \times \text{centrifuge tube contents less cell volume}}$$

Since we have injected a uniform amount of dye into persons of different weight and therefore of different blood volumes, it follows that the concentration of the dye in the blood samples obtained two minutes after injection should show considerable variation, and that it would be impossible to compare the corrected colorimeter readings of different persons with one another unless these readings were reduced to some arbitrary standard blood volume. The standard blood volume selected arbitrarily and purely for convenience for the purpose of this paper is 7,000 c c. Thus in the foregoing the corrected colorimetric reading of the "two minute sample" of blood is 18.8 per cent of an 0.0075 per cent solution of the dye, from which the blood volume of 7,070 c c can be calculated. If now we reduce this to our standard blood volume of 7,000 c c it is evident that it is necessary to multiply the reading 18.8 by 7,070 and divide the result by 7,000 which gives 19.1 per cent of an 0.0075 per cent solution. This figure (19.1) is necessarily a mathematical constant since it expresses the concentration of a fixed amount of dye (100 mg.) injected into a fixed volume (7,000 c c).

Occasionally in large persons we have injected 150 mg. of dye instead of 100 mg. in which case we multiply the reading, which has been reduced to the standard blood volume of 7,000 c c, by 100 and divide the result by 150, thus standardizing the dosage as well as the blood volume. After these corrections have been made it is possible to compare the rates of elimination of the dye from the circulation of different persons one with the other. Charts 1, 2 and 3 show curves representing the rate of elimination of the dye from the blood streams of the patients whom we have studied. Since the liver is presumably acting on a progressively decreasing amount of dye remaining in the circulation, it would seem correct to use as the ordinates of the curves the logarithms of the different concentrations of the dye.

Chart I shows the logarithmic curves of the concentration of the dye four and eight minutes after injection of 100 mg. of rose bengal (when computed on the basis of a standard blood volume of 7,000 c c), in a series of twenty-four cases clinically free from liver disease selected from the medical wards of the University of California Hospital. In these cases the average concentration of the dye four minutes after injection was 0.00116 per cent, varying between 0.00137 per cent and 0.00060 per cent, and eight minutes after injection the average concentration was 0.00085 per cent, varying between the limits of 0.00102 per cent and 0.00061 per cent.

Chart 2 shows the logarithmic curve of a series of thirteen cases with clinical evidence of liver disease. In this group the average concentration of the dye in the blood four minutes after injection was

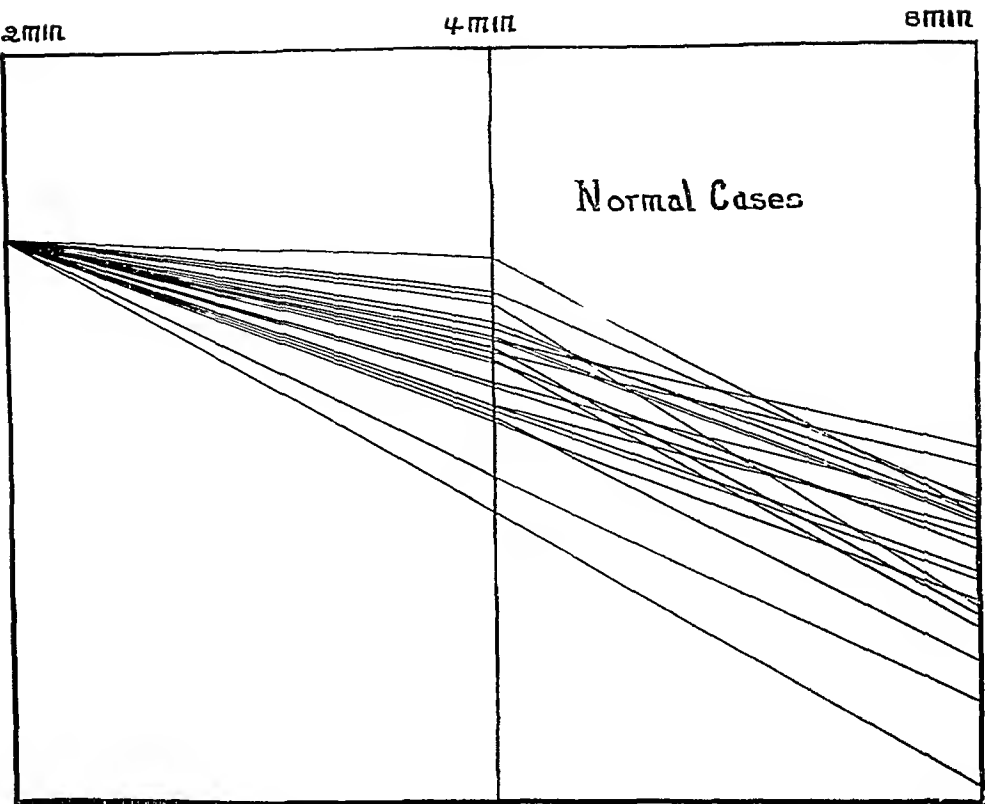


Fig 1—Logarithmic curves of the concentration of rose bengal in the circulation of normal persons after the intravenous injection of 100 mg of the dye. Colorimetric readings have been corrected to an arbitrary blood volume of 7,000 cc for comparison.

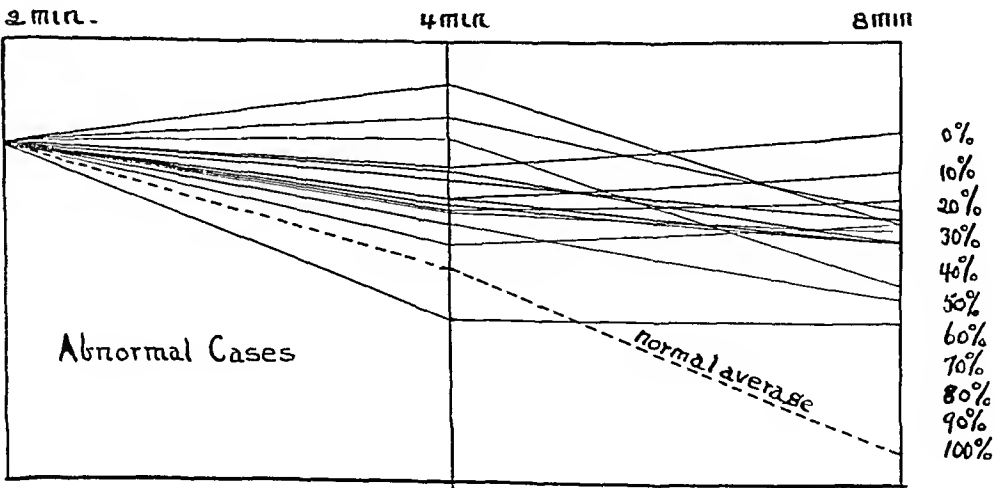


Fig 2—Curves obtained on a group of patients with liver disease. Percentages at the right of chart express the suggested function of the liver.

0.00136 per cent, varying between 0.00160 and 0.00116 per cent, and eight minutes after injection the average concentration was 0.00124 per cent, varying between 0.00144 and 0.00116 per cent. It can be seen that the average concentration of the dye in the blood four and eight minutes after injection in the group with liver disease is considerably higher than in the normal group, and that the lowest concentration reached at four and eight minutes in the abnormal group is considerably above the highest variation in the normal group. The group with liver disease is composed of the following cases:

#### ABSTRACT OF ABNORMAL CASES

CASE 14—Carcinoma of head of the pancreas, complete biliary obstruction, no ascites

CASE 15—Cirrhosis of the liver, end stage of Banti's disease, marked ascites, confirmed at operation

CASE 16—Syphilis of the liver, jaundice, ascites

CASE 17—Carcinoma of the head of the pancreas, with complete obstruction, confirmed at operation

CASE 18—Cirrhosis of the liver, jaundice, ambulatory

CASE 19—Cirrhosis of the liver, marked ascites

CASE 21—Cirrhosis of the liver, marked ascites, jaundice

CASE 30—Enlarged liver, mediastinal tumor, question of metastatic malignancy of the liver

CASE 31—Advanced cirrhosis, von Jaksch disease, confirmed by necropsy

CASE 33—Cirrhosis with marked ascites

CASE 39—Moderately advanced cirrhosis of the liver with ascites

CASE 20—Postoperative cholecystitis and cholelithiasis. Probable cirrhosis

CASE 22—Cancer of rectum, extensive liver metastases

This group includes persons with complete biliary obstruction, where no elimination of the dye through the liver could be expected.

Chart 3 includes a group of seven patients who have a history of probable chronic cholecystitis. This group includes men and women who were apparently in good health and ambulatory, but who could not be classified as normal because of the possibility of liver disease. It is not surprising that persons appear in this group who show curves which may well be classified as normal on the basis of the test that has been outlined in the foregoing. These cases are numbered 4, 13, 34, 35, 36, 37 and 38. The curve in Case 4 lies just above the upper limit of variation of the normal group but can hardly be considered as definitely abnormal. The border-line group includes

CASE 4—Chronic passive congestion

CASE 13—Chronic interstitial nephritis and cardiac failure, with general anasarca, chronic passive congestion of the liver

CASE 34—Chronic cholecystitis

CASE 35—Chronic cholecystitis

CASE 36—Cirrhosis of the liver (seen three years before at operation), patient ambulatory and apparently well

CASE 37—Chronic cholecystitis and cholelithiasis

CASE 38—Chronic cholecystitis

This last group of cases illustrates the probability that a considerable degree of liver damage must exist before any variation from a group of normal persons can be determined, and that although a pathologic condition of the liver tissue may be determined microscopically, that enough normal parenchyma exists to carry on the various functions of the organ. This same limitation is seen in the permeability test of the kidney with phenolsulphonephthalein.

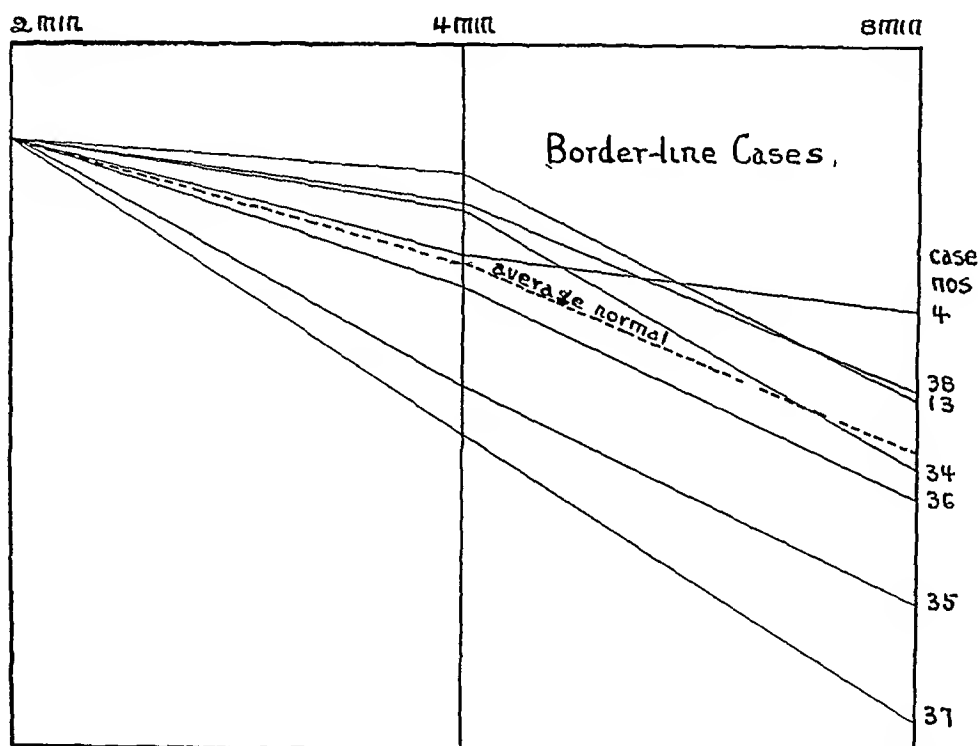


Fig 3—Curves obtained on a group of border-line cases with possible liver disease

### CONCLUSIONS

1 In normal persons, following the injection of a given amount of rose bengal into the circulation, the concentration of the dye computed under standard conditions of dosage and blood volume does not exceed certain limits at four and eight minutes after the time of injection.

2 In abnormal cases, where evidence of liver disease can be demonstrated clinically, the concentration of the dye in the circulation computed under standard conditions of dosage and blood volume, at four and eight minutes from the time of injection, exceeds the limits of concentration of the normal cases. Complete biliary obstruction, which

can be determined by other clinical tests, causes a retention of the dye in the blood stream

3 When it can be shown that the rate of elimination of rose bengal from the circulation, after injection, is reduced, or in other words, when the concentration of the dye at four and eight minutes after injection exceeds the normal limits, a certain degree of liver dysfunction may be assumed to exist in the absence of complete biliary obstruction

4 A rough estimate can be formed from the concentration of the dye remaining in the circulation at four and eight minutes after injection of the extent of the liver disease



# STUDIES IN THE DIASTATIC ACTIVITY OF THE BLOOD, WITH A CONSIDERATION OF ITS VALUE IN CLINICAL DIAGNOSIS \*

I C BRILL, M D

PORTLAND, ORE

In 1917, Myers and Killian<sup>1</sup> published a simple, delicate and accurate method for estimating the diastatic activity of the blood. Briefly, the method consists in allowing a known quantity of blood (2 c c) to act on a known quantity of pure soluble starch (1 c c of a 1 per cent solution = 10 mg) for a definite length of time (fifteen minutes) in a water bath at 40 C. The glucose thus produced by the blood diastase is then determined by the Myers and Bailey method.<sup>2</sup> A control is run in a second tube to determine the original glucose contained in the 2 c c of blood, which is deducted from the total glucose found in the first tube. The results are recorded in terms of the percentage of the starch (10 mg) transformed to reducing sugar (calculated as glucose) by the 2 c c of blood employed. Thus, by a "diastatic activity of 15" is meant that 15 per cent of the 10 mg of starch was converted into glucose by the diastase in the 2 c c of blood used.

In introducing their method, Myers and Killian state that, concerning the question of blood diastase in human diabetes, "Foster, Bainbridge and Beddard, Schlesinger, Wynhausen, Ghedini, and Stocks, were unable to come to any conclusions, though Loewi regarded the diastase of considerable importance, and Moeckel and Rost state, apparently from meager data, that the diastatic activity of the blood in human diabetes is almosts always higher than normal." In a study of blood diastase, on a series of normal and miscellaneous hospital cases, Myers and Killian found that in normal blood the diastatic activity, as estimated by their method, varied from 15 to 25. In a series of thirteen cases of diabetes they found the diastase much increased, the figures varying from 39 to 74. In eleven of 23 cases of nephritis they found the diastase to range from 30 to 52. The fact that these cases, in which a high blood diastase was noted, also showed a hyperglycemia, suggested to the authors the idea "that the increased diastatic activity in both diabetes and nephritis (as shown by the analyses of the blood) may be

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\* From the Medical Clinic of the Peter Bent Brigham Hospital, Boston

1 Myers, V C, and Killian, J A. Studies on Animal Diastases, J Biol Chem 29 179 (March) 1917

2 Myers, V C, and Bailey, C V. The Lewis and Benedict Method for the Estimation of Blood Sugar with Some Observations Obtained in Disease, J Biol Chem 24 147 (Feb) 1916

the important factor in the production of the hyperglycemia in these conditions" As a result of their studies, Myers and Killian concluded that "a fall in the blood diastase would appear to afford a more reliable guide to the efficacy of the dietetic treatment in diabetes than either the blood sugar or urine sugar Furthermore, an increase in blood diastase may constitute a very early sign of impending diabetes"

DeNiord and Schreiner<sup>3</sup> failed to confirm the findings of Myers and Killian Using the Myers and Killian method for blood diastase estimation, DeNiord and Schreiner reported their observations on six cases of diabetes, all of which showed a low or normal blood diastase Since these cases were syphilitic, and the results so opposed to the work of Myers and Killian, DeNiord and Schreiner suggested that a low diastatic activity in diabetes was possibly indicative of an associated syphilitic infection

Block,<sup>4</sup> after summarizing the literature on the subject, arrived at the conclusion that the determination of the diastatic activity of the blood was of but limited clinical significance, that the normal variations were exceedingly great, and that unless the diastatic activity of the blood was increased to a value of 100<sup>5</sup> or more it could not be regarded of diagnostic import However, in Block's opinion, an increase in blood diastase to 100 or more is indicative of pancreatic disease Block included in this connection, diseases of the neighboring organs affecting the pancreas secondarily, such as a duodenal ulcer perforating into the pancreas or obstructing the pancreatic duct, but he did not include diabetes In the latter instance he found the reports conflicting, and his own observations did not warrant him to regard the blood diastase of any significance in this disease

The present study was undertaken in order to establish the clinical value of blood diastase determinations, made according to the method of Myers and Killian, in diabetes, nephritis and diseases of the pancreas For this purpose the following plan of investigation was carried out

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3 DeNiord, H H, and Schreiner, B F Diastatic Activity of the Blood in Cancer, Syphilis and Diabetes, *Arch Int Med* **23** 484 (April) 1919

4 Block, W Die praktische Verwertbarkeit der Amylase- (Diastase-) Bestimmung in Blut und Urin für die Diagnostik der verschiedensten pathologischen Zustände, *Ztschr f klin Med* **93** 381, 1922

5 Block does not state clearly what unit of diastatic activity he used, but from the text one may infer that he employed Wohlgemuth's (*Biochem ztschr* **9** 1 [Jan] 1908) colorimetric method, which is based on an iodine starch reaction, and the figure 100 refers to the number of cubic centimeters of 1 per cent starch solution that could be converted into dextrin by 1 c.c. of blood serum in twenty-four hours at 40 C From a comparative study of the results on Block's normal subjects, obtained by this method, and my normal figures obtained by the Myers and Killian method, I regard the value of 100 by Wohlgemuth's method to be equivalent to about 50 or 60 by the Myers and Killian method

## METHOD OF INVESTIGATION

1 The diastatic activity of normal human blood was determined in thirty-five cases in order to establish a normal standard. These estimations included observations on the effect of food and time of day on blood diastase in normal subjects.

2 The diastatic activity of diabetic blood was determined in twenty-five cases. Observations were also obtained on the immediate effect of food and insulin on the blood diastase in diabetes.

3 The diastatic activity of dog's blood was determined in four normal and two depancreatized dogs.

4 The diastatic activity of human blood was determined in one case of carcinoma of the pancreas.

5 The diastatic activity of human blood was determined in five cases of nephritis.

The results of this study are tabulated.

## DIASTASE IN NORMAL HUMAN BLOOD

For the purpose of establishing an accurate normal standard two groups of cases were studied. One group consisted of thirteen normal

TABLE 1—*The Diastatic Activity of Normal Human Blood\**

Case	Diagnosis	Blood Sugar	Units of Diastatic Activity	Remarks
1	B Normal	0.113	10	
2	I Normal	0.140	10	
3	C Normal	0.130	11	
4	S Normal	0.140	6	
5	A Normal	0.112	7	
6	Student Normal	0.091	19	
7	Student Normal	0.090	12	
8	Student Normal	0.099	16	
9	C Normal	0.110	8	
10	K Normal	0.123	11	
11	D Normal	0.100	6	
12	S Normal	0.109	12	
13	D Normal	0.102	8	
14	C Duodenal ulcer	0.114	14	
15	B Duodenal ulcer	0.117	12	
16	R Duodenal ulcer	0.091	9	
17	S Duodenal ulcer	0.109	17	
18	Y Duodenal ulcer	0.099	9	
19	B Rheumatic pericarditis	0.113	14	Convalescent Practically well
20	J Typhoid	0.107	24	Convalescent Practically well
21	B Duodenal ulcer	0.100	11	
22	F Chronic diarrhea	0.113	15	
23	L Duodenal ulcer	0.125	18	Diagnosis questionable
24	H Duodenal ulcer	0.104	23	
25	L Duodenal ulcer	0.099	13	Diagnosis proved at operation and at necropsy
26	N Pneumonia	0.130	21	Convalescent Practically well
27	G Medical observation	0.099	16	
28	P Neurosis	0.094	14	
29	Ch Respiratory infection	0.107	13	Convalescent Practically well
30	Ch Pulmonary tuberculosis	0.107	18	Inactive process
31	Sh Asthma bronchial	0.084	16	No recent attacks
32	G Pelvic tumor	0.097	15	Proved to be carcinoma
33	X Coma	0.174	6	Due to illuminating gas poisoning
34	X Acute diarrhea	0.192	18	Young child
35	De Medical observation	0.124	2	

\* Cases 14 to 35 represent a group of miscellaneous hospital cases which for the purpose of this investigation may be regarded as essentially normal.

persons composed of students and members of the hospital staff. The other group consisted of twenty-two miscellaneous hospital patients, of whom all but two showed a normal blood sugar. The results are recorded in Table 1.

As can be seen from examining the figures in this table, the diastatic activity in normal blood may vary between 2 and 24. Myers and Killian,<sup>6</sup> give from 15 to 25 as the normal limits. In repeating blood diastase estimations on the same person at intervals of a week or more, I obtained much more constant figures, five units being the highest variation noted. It appears, therefore, that, although in different persons blood diastase may vary between wide limits, in the same subject the variations are much less marked.

TABLE 2—*The Effect of Food on the Diastatic Activity of Normal Human Blood*

Time	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6	
	Blood Sugar	Units of Diastatic Activity	Blood Sugar	Units of Diastatic Activity	Blood Sugar	Units of Diastatic Activity	Blood Sugar	Units of Diastatic Activity	Blood Sugar	Units of Diastatic Activity	Blood Sugar	Units of Diastatic Activity
Fasting	0.102	8	0.100	6	0.117	11	0.107	24	0.125	18	0.130	21
½ hour after meal	0.137	9	0.108	4								
1 hour after meal	0.136	4	0.108	6								
1½ hours after meal	0.113	8	0.124	2	0.122	12	0.103	23	0.140	22	0.115	20
2 hours after meal	0.113	7										

Table 2 gives the results of experiments which were made to show the effect of food on the diastatic activity of the blood in normal subjects. The figures obtained in these experiments seem to indicate that normal blood diastase is not affected by food or time of day. Those findings are in accord with the observations of Carlson and Luckhardt,<sup>7</sup> who performed similar experiments on animals.<sup>8</sup>

<sup>6</sup> Myers, V. C. *Practical Chemical Analysis of Blood*, Ed. 2, St. Louis, C. V. Mosby Co., 1924, p. 84.

<sup>7</sup> Carlson, A. J., and Luckhardt, A. B. *On the Diastase in the Blood and the Body Fluids*, *Am. J. Physiol.* **23**: 148 (Dec.) 1908.

<sup>8</sup> Carlson and Luckhardt studied blood diastase in a variety of animals, including dogs, cats, rabbits, pigs, sheep, goats and pigeons. They measured the concentration of the diastase in the serum "by (1) the rate of clearing and (2) by the rate of complete disappearance of erythrodextrin in the starch solution. The starch solution and serum or lymph were usually mixed in the proportion of from 5 to 0.1 cc and kept in thermostat at 38° C." The unit of diastatic activity used by these authors is not clearly defined. The concentration of the blood diastase was recorded as "equal," "greater" or "less" than some assumed standard, thus indicating respectively an equal, shorter, or longer time required to clear the starch solution at the given temperature (38° C.) and at the given proportion of starch serum mixture (5 to 1 cc).

## BLOOD DIASTASE IN DIABETES

Table 3 shows the results obtained in a series of twenty-five cases of diabetes. They were all typical cases with the exception of one patient (Case 25) who came in to the hospital with symptoms of acromegaly and pituitary disease. An examination of the results recorded in this table reveals the fact that, with the exception of the

TABLE 3—*The Diastatic Activity of the Blood in Diabetes*

Case	Blood Sugar	Units of Diastatic Activity	Remarks
1 O	0.149	12*	Urine sugar + (mild case)
2 O D	0.214	12	Urine sugar ++
3 L	0.256	11*	Urine sugar ++
4 R	0.380	15*	Urine sugar +++
5 B	0.310	14*	Urine sugar ++++
6 F	0.295	14*	Urine sugar +
7 R	0.245	3*	Urine sugar + (traces)
8 W	0.185	10*	Urine sugar ++
9 P	0.221	18	Urine sugar +++
10 R	0.425	19	Urine sugar ++++
11 MeL	0.136	9*	Urine sugar +
12 Sh	0.250	17*	Urine sugar 1.8 per cent
13 W	0.240	6*	Urine sugar 6 per cent
14 K	0.390	25*	Urine sugar 1.4 per cent
15 R	0.250	26*	Urine sugar ++
16 H	0.221	16*	Under treatment with insulin Only traces of sugar in urine
17 C	0.367	18*	
18 T	0.198	18*	
19 X	0.353	14	
20 G	0.363	10*	Urine sugar 7 per cent
G	0.375	10.6*	Urine sugar 6 per cent
21 S	0.263	10*	Urine sugar 5 per cent
22 B	0.540	12	Urine sugar +
B	0.222	17	Urine sugar +++
23 Bl	0.185	23	Urine sugar neg
24 P	0.340	15	Urine sugar ++
25 R	0.230	32	Urine sugar ++++
			Evidence of pituitary tumor with acromegaly symptoms Urine sugar ++

\* Blood drawn during fasting state. Others were examined in from 1 to 2 hours after meals.

TABLE 4—*The Effect of Food on the Diastatic Activity of the Blood in Diabetes*

Time	Case 1		Case 2	
	Blood Sugar	Units of Diastatic Activity	Blood Sugar	Units of Diastatic Activity
Fasting	0.363	10	0.300	14
One-half hour after meal	0.425	9.4		
1 hour after meal	0.483	11.4		
1½ hours after meal	0.487	7	0.540	12

one typical case, the diabetics in this group yielded figures for blood diastase essentially like those obtained in our series of normal persons. Syphilis was excluded as a factor, since the histories justified such exclusion in all cases but one, and the Wassermann reaction was negative in every instance.

Table 4 records the results of experiments which were made to show the effect of food on the blood diastase in diabetes. The results obtained in this study are much like those seen in similar experiments

on normal persons. It is interesting to note that although the blood sugar rose considerably after the patient had taken food, the blood diastase remained either unaffected or was even lowered. These results speak against any relationship between hyperglycemia and increased diastatic activity of the blood.

#### EFFECT OF INSULIN

Table 5 records the results of experiments made to demonstrate the effect of insulin on the diastatic activity of the blood in diabetes. It will be seen from an examination of these figures<sup>1</sup> that although the blood sugar showed a marked and steady reduction in each instance,

TABLE 5—*The Effect of Insulin on the Diastatic Activity of the Blood in Human Diabetes*

	Case 1		Case 2	
	Blood Sugar	Units of Diastatic Activity	Blood Sugar	Units of Diastatic Activity
Dec 17, 1923 Six weeks before the insulin experiment, Case 1 was examined in the Outdoor Department with these findings	0.300	11		
Experiment Jan 29, 1924				
Before insulin	0.540	10	Before insulin	0.353 14
½ hour after 10 units of insulin	0.465	16	20 units given	
1 hour after 10 units of insulin	0.395	17	1 hour later	0.166 19
1½ hours after 10 units of insulin	0.357	17	1½ hours later	0.102 14
2 hours after 10 units of insulin	0.353	13		
2½ hours after 10 units of insulin	0.342	12	2½ hours later	0.111 14
Feb 6 After receiving one week's careful dietary treatment in the ward, with a sugar free urine, Case 1, on reexamination showed	0.220	17		

there was no corresponding change in the blood diastase. On the whole, the variations noted were not unlike those seen in similar serial determinations in both normal and diabetic subjects who had not received insulin, and the results suggest that insulin is without significant influence on the diastatic activity of the blood in diabetes. Myers,<sup>6</sup> on the other hand, reported a similar experiment in one case, noting a slight reduction in the blood diastase after insulin.

#### BLOOD DIASTASE IN NORMAL AND IN DEPANCREATIZED DOGS

The blood diastase in four normal dogs was estimated by the Myers and Killian method. The pancreas was then removed in two of these dogs, and their blood again examined for the diastatic activity. The results of these experiments are recorded in Table 6. As may be seen from an examination of these results, the diastatic activity of normal dog's blood is from three to six times as high as the diastatic activity of normal human blood. The blood diastase estimations made in the

depancreatized dogs yielded figures slightly lower than those obtained in the same dogs before the operation or in the other normal dogs

These findings correspond with the observations of Carlson and Luckhardt,<sup>7</sup> who performed similar experiments on two cats. Carlson and Luckhardt were able to keep these animals alive for eight and eleven days respectively. Frequent diastase determinations on these animals showed, in one animal, a slight reduction in the diastatic activity during

TABLE 6—*The Diastatic Activity of the Blood in Normal and in Depancreatized Dogs*

Experiments		Blood Sugar	Units of Diastatic Activity
Dog 1	Normal	0.097	73
Dog 2	Normal	0.107	87
Dog 3	Normal	0.107	77
Dog 4	Normal	0.116	77
Dog 1	Immediately after total extirpation of pancreas	0.222	65
Dog 2	Immediately after total extirpation of pancreas	0.200	72
Dog 2	Five hours after operation. Dog has completely recovered	0.193	67
Dog 1	Two days after operation. Dog apparently completely recovered from operation and is running around like a normal dog	0.346	55

the first five days after the operation, with a return to normal on the eighth day, in the other animal the diastatic activity remained normal till its death on the eleventh day after the operation. However, Myers and Kilhan report a decided increase in the blood diastase in one depancreatized dog, and Milne and Peters<sup>9</sup> report increases in the blood serum diastase in a large series of dogs after complete or partial removal of the pancreas.<sup>10</sup>

#### BLOOD DIASTASE IN DISEASE OF THE PANCREAS

It has been seen that pancreatectomy did not immediately affect the concentration of the blood diastase to any extent in two dogs. To

TABLE 7—*The Diastatic Activity of the Blood in Pancreatic Disease*

Experiments		Blood Sugar	Units of Diastatic Activity
1	Human. Carcinoma of head of pancreas. Determination made 2 days after operation	0.125	13
2	Same as 1, four days after operation	0.130	10
3	Dog*. Pancreatic ducts ligated 10 weeks before	0.098	73
4	Same as 3, two days later	0.111	98

\* The animal went through the usual period of emaciation with recovery and is now well nourished, lively, and behaves like a normal dog, with the exception of having large bulky stools.

9 Milne, L. S., and Peters, H. LeB. Observations of the Glycolytic Power of the Blood and Tissues in Normal and Diabetic Conditions, *J. M. Res.* **26**: 415 (July) 1912.

10 The method for diastase estimations employed by Milne and Peters is similar to that of Myers and Kilhan, but not so accurately standardized with respect to quantity of reagents and time of incubation.

determine the effect of a diseased pancreas on the diastatic activity of the blood, estimations of the blood diastase were made in one human case of pancreatic carcinoma found at operation, and in one dog in which the pancreatic ducts had been ligated ten weeks before. The results of these experiments are recorded in Table 7.

It will be seen that no significant changes in the blood diastase were noted in these two instances. However, Myers and Killian,<sup>6</sup> reported a moderate increase in the blood diastase in two cases of pancreatic carcinoma and in two cases of pancreatitis, and it has also already been stated that Block<sup>4</sup> regarded a marked increase in the blood diastase as indicative of pancreatic disease. The diagnostic value of blood diastase determinations in suspected pancreatic disease is therefore at present uncertain.

#### BLOOD DIASTATIC IN NEPHRITIS

Myers and Killian report a decided increase in the blood diastase in eleven of twenty-three cases of nephritis in human beings. Fitz,<sup>11</sup> experimenting on rabbits in which he produced an acute nephritis by

TABLE 8—*The Diastatic Activity of the Blood in Nephritis*

Case	Diagnosis	Blood Pressure	Phthalein Excretion per Cent	Blood Urea Nitrogen Mg per 100 C c	Blood Sugar	Units of Diastatic Activity
1	Chronic nephritis with hypertension	250/145	0	134	0.187	34
(7 days later)	Uremia		0	203	0.166	55*
2	Chronic nephritis	140/95	Trace		0.136	25
3	Subacute nephritis with features of nephrosis (Epstein)	126/90	35	11	0.111	18
4	Chronic nephritis with hypertension	180/120	15	33	0.150	15
5	Chronic nephritis with hypertension	230/140	Trace	12	0.115	22

\* Died 2 days after this determination.

means of uranium nitrate, obtained an increase in the blood diastase (estimated by the Wohlgemuth method) in five out of seven rabbits in which kidney lesions were demonstrated histologically. In the present study the diastatic activity of the blood was estimated in five cases of various types and degrees of nephritis, and the results are recorded in Table 8.

It will be seen that only in one case was a marked increase in the blood diastase found. Two estimations were made in this case at an interval of seven days. At the time of the second examination the patient was in uremic stupor. Although the blood diastase rose from 34 to 56, the blood sugar, at the same time fell from 0.187 to 0.166.

<sup>11</sup> Fitz, R. The Relation Between Amylase Retention and Excretion and Non-Protein Nitrogen Retention in Experimental Uranium Nephritis, *Arch Int Med* **15** 524 (April) 1915.



Here again the figures speak against any relationship between glycemia and blood diastase. The results, however, seem to indicate that while blood diastase determinations can be of but limited value in the diagnosis of nephritis, they may prove of prognostic value, a steady rise in blood diastase pointing to an unfavorable progress of the disease. Further studies along this line seem desirable.

#### INCIDENTAL OBSERVATIONS

During the progress of this investigation several problems arose in connection with the technic, which suggested certain experiments. Occasionally it was found necessary to keep a blood specimen from half to one hour before it was possible to begin the diastase determination. In order to ascertain what effect such delay had on the diastatic activity, several experiments were carried out, the results of which are recorded in Table 9. It will be seen from these results that, although

TABLE 9—*The Stability of the Diastatic Enzyme and its Distribution in the Various Blood Components*

Experiments	Blood Sugar	Units of Diastatic Activity
1 Determination immediately after drawing blood from vein	0.425	19
2 Same blood as 1, kept 24 hours in refrigerator	0.415	11 = 40% loss
3 Immediate determination	0.353	15.4
4 Same as 3, kept 24 hours in refrigerator	0.323	15.4 = no loss
5 Immediate determination	0.125	18
6 Same as 5, kept 2 hours in refrigerator	0.115	18 = no loss
7 Immediate determination	0.387	17
8 Same as 7, kept 1 hour at room temperature	0.387	15 = 12.5% loss
9 Whole oxalated blood	0.222	17
10 Same as 9 without oxalate	0.222	17
11 Whole oxalated blood	0.187	34
12 Plasma from same blood as 11	0.166	34
13 Serum from same blood as 11	0.166	37
14 Whole oxalated blood	0.510	10
15 Serum from same blood as 14	0.520	23

a delay of one hour is not likely to result in serious error, it is best to begin the determination within fifteen minutes to half an hour after drawing the blood from the vein.

Another question arose concerning the method of collecting blood, with special reference to the effect which oxalate might have on the enzyme action. Table 9 shows that the oxalate used in this work was without effect on the diastatic action of the blood. Two interesting observations, however, were made concerning the difference in diastatic activity of whole oxalated blood, blood plasma (derived from oxalated blood), and blood serum (derived from clotted blood). Equal quantities (2 c.c.) were used from each of these blood mixtures, and the samples subjected to the same laboratory conditions at the same time.

It will be seen that, although the blood plasma (oxalated) yielded the same results as the whole oxalated blood, yet the blood serum showed a higher diastatic activity than the corresponding whole blood. The

degree of increased activity varied from a very slight gain to more than twice the activity of the corresponding whole blood. This latter observation is interesting, as it suggests the possibility that new diastase may be produced during the process of clotting, perhaps from diastatogenic enzymes which become activated during the process of clotting. It was noted that the degree of increased activity in serum diastase depended on the method of separating the serum, whether the blood was centrifuged immediately on clotting, or whether the serum was permitted to separate slowly. In the latter instance the increase in diastase was greater. Similar observations were noted by Carlson and Luckhardt,<sup>7</sup> although the variations reported by these investigators were less striking. It appears, from these findings, that serum diastase may vary with factors not entirely under control, and is, therefore, less desirable for comparative studies.

#### SUMMARY AND CONCLUSIONS

1 The diastatic activity of normal human blood was estimated by the Myers and Killian method in thirty-five cases. The figures obtained varied between 2 and 24.

2 The diastatic activity of diabetic blood was estimated, by the same method, in twenty-four cases of human diabetes. The figures obtained were essentially similar to those observed in the normal series, varying between 3 and 26. In one atypical case of diabetes a blood diastase of 32 was observed. The results, furthermore, indicated that a low blood diastase in diabetes was in no way suggestive of an associated syphilitic infection.

3 No significant changes were noted in the diastatic activity of the blood, in serial determinations, on either normal or diabetic subjects, before and after they had taken food.

4 The injection of insulin in two diabetic subjects produced no significant change in the concentration of their blood diastase.

5 There was no correlation noted between the concentration of the blood diastase and the blood sugar concentration in either diabetic or nephritic subjects.

6 The diastatic activity of the blood in two depancreatized dogs was slightly lower than normal during the first two days after the operation.

7 A normal blood diastase was observed in one case of carcinoma of the head of the pancreas. A normal diastatic activity was also obtained in the blood of a dog, in which the pancreatic ducts had been ligated ten weeks before, and in which symptoms of pancreatic insufficiency had been noted.

8 A decided increase in blood diastase was obtained in one case of severe nephritis. The results suggested the possibility that serial determinations in severe nephritis might prove of prognostic value.

9 Estimation of the diastatic activity of the blood, as determined by the method of Myers and Killian, yielded no information of clinical value in the cases of diabetes and in the one case of pancreatic carcinoma studied.

# BASAL PULSE RATE AND PULSE PRESSURE CHANGES ACCOMPANYING VARIATIONS IN THE BASAL METABOLIC RATE

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The rôle played by the blood and circulatory system in the gaseous metabolism of the body has constituted the subject of numerous investigations. These fall naturally into two groups. One comprises researches into the oxygen carrying capacity of the hemoglobin and the other group embraces studies on the volume flow of blood. The necessity for a wide range of functional adaptation is apparent when we recall that during severe exercise the amount of oxygen required may be seven or eight times greater than that which suffices under resting conditions.

Barcroft, Haldane and their co-workers demonstrated the reserve power of the hemoglobin by showing that under ordinary conditions oxyhemoglobin gives up approximately only one-third of its oxygen to the tissues but may, when the demand exists, give up much more. Studies on the volume flow of blood, which have been facilitated by the nitrous oxid method of Krogh and Lindhard, indicate that the volume flow of blood may be increased threefold or fourfold during the performance of work. These investigations of two entirely different methods of varying the rate of oxygen transportation by the blood suggest that there exists the mechanism which would provide considerable liability of adaptation. One or possibly both methods are employed whenever larger volumes of oxygen are required under either normal or pathologic conditions. Unfortunately the methods employed in demonstrating the existence of the functions described in the foregoing do not permit of easy clinical application.

Utilizing the respiration calorimeter, it is now possible to measure the oxygen consumption with sufficient accuracy for clinical purposes. Quantitative variations in the amount of work done by the circulatory system in performing its function of transporting oxygen are roughly represented by pulse rate and blood pressure changes, which presumably serve the purpose of altering the volume flow of blood. This report, based on 600 basal metabolic rate estimations, constitutes an endeavor to ascertain the relationship between oxygen consumption and circulatory system activities by the utilization of statistical methods.

The procedure here employed consisted in ascertaining the basal pulse rate simultaneously with determination of the basal metabolic rate. Frequent pulse readings were made throughout the two ten minute periods during which the patient was connected with the respiration

calorimeter. A reading of the blood pressure was made in the resting interval between the breathing tests. This "basal blood pressure," as pointed out by Addis,<sup>1</sup> is lower than the "daytime pressures" and represents more accurately the true status of the person's pressure. The blood pressure readings were recorded, in order to ascertain whether or not the pressure showed any such relationship to metabolic rate as was known to exist between pulse rate and basal metabolic rate.

#### PULSE RATE

A rapid pulse in a thyrotoxic patient with a high basal metabolic rate is a frequent clinical finding. This association of increased heart rate with elevated metabolic rate has been the subject of repeated comment in the literature. Sturgis and Tompkins<sup>2</sup> reported a study of the correlation of basal metabolism and pulse rate in 154 patients with hyperthyroidism. The opposite finding, a slow pulse rate and low metabolic rate obtaining in hypothyroid persons, is an association commonly observed by workers in clinical calorimetry. That a certain amount of parallelism exists between pulse rate and metabolic rate has been generally recognized. Benedict and Cathcart<sup>3</sup> obtained a very close relationship between the changes in metabolism and pulse rate of a bicycle rider. They report "It soon became apparent that the pulse rate, even during severe muscular work, very closely followed the amount of energy output, an observation that is fully in accord with the values secured with normal resting subjects which show that the pulse rate and the total metabolism are intimately related." That this association is purposeful, in that the increased number of heart beats serves to hasten the rate of blood flow when more oxygen is required by the tissues, has been demonstrated by many investigators.

#### PULSE PRESSURE

There are numerous studies reported of the blood pressure in thyrotoxic states since the observations of Gross,<sup>4</sup> in 1900, who found increased systolic pressure in all of his seven patients. The largest

1 Addis, Thomas. Blood Pressure and Pulse Rate Levels, *Arch Int Med* **29** 539 (April) 1922.

2 Sturgis, C. C., and Tompkins, E. H. A Study of the Correlation of the Basal Metabolism and Pulse Rate in Patients with Hyperthyroidism, *Arch Int Med* **26** 467 (Oct.) 1920.

3 Benedict, G., and Cathcart, E. P. Muscular Work, A Metabolic Study with Special Reference to the Efficiency of the Human Body as a Machine, No 187, Carnegie Inst., Washington, 1913.

4 Gross, A. Zur Kenntniss der pathologischen Blutdruckänderungen nach Beobachtungen von Weil, *Deutsch Arch f klin Med* **74** 297, 1902.

series is that of Plummer,<sup>5</sup> who records increased systolic pressure with increased pulse pressure. Many conflicting statements are encountered in the literature on this subject and are due, probably, to two factors: first, the stage of the disease and state of cardiac compensation are not considered and, second, the pressures were taken under varying daytime conditions. One fact seems to be generally established, especially by the later writers, namely, that the pulse pressure is greater than normal, i. e., more than 50 per cent of the diastolic pressure. This fact is especially stressed by Taussig,<sup>6</sup> who compares the circulatory abnormalities of exophthalmic goiter with those of aortic regurgitation. Harris<sup>7</sup> has recently pointed out the unusual association of rapid pulse and increased pulse pressure and considers it quite characteristic of thyrotoxicosis, since "a frequent pulse in any other condition is usually accompanied by a small pulse pressure." The characteristic sphygmomanometric finding in thyrotoxic states, then, is widened pulse pressure. Accepting this and recalling the normal or low systolic, relatively high diastolic and lessened pulse pressure in hypothyroidism, the idea presents itself that a relationship may exist between pulse pressure and metabolic rate. It was determined, therefore, to limit this study to those blood pressure changes represented by the difference between systolic and diastolic pressure, namely, pulse pressure.

#### THE DATA

The data constituting the basis of this study were compiled from 600 determinations of the basal metabolic rate. These determinations were made in the departments of clinical calorimetry at St. Luke's Hospital, Stanford University Hospital, the San Francisco Hospital and in private practice. All the work was done with the apparatus described by Benedict as the portable respiration calorimeter. Approximately half of the determinations were made by me, the others by physicians serving their first and second postgraduate years in the before mentioned hospitals.

The subjects furnishing these data were not selected in any way, and the only exclusions were patients who showed pathologic conditions in the cardiovascular-renal system affecting the pulse rate or blood pressure. Table 1 shows the age and sex distribution among the subjects. Ninety-five per cent were between the age of 25 and 55 years. Exclusion of those above 55 seemed advisable because of the alterations in blood

<sup>5</sup> Plummer, H. S. Blood Pressure and Thyrotoxicosis, *Tr. A. Am. Phys.* **30** 450, 1915.

<sup>6</sup> Taussig, A. E. Some Blood Pressure Phenomena in Exophthalmic Goiter, *Tr. A. Am. Phys.* **31** 121, 1916.

<sup>7</sup> Harris, I. The Pulse Pressure in Exophthalmic Goiter, *Brit. M. J.* **1** 630 (April 14) 1923.

TABLE 1—*Age and Sex Distribution*

Basal Metabolic Rate, per Cent	Female	Male	Years									
			15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64
70.1 to 80	6	3	0	1	0	0	3	2	3	0	0	0
60.1 to 70	17	5	0	5	4	2	4	3	2	1	0	1
50.1 to 60	23	13	0	3	7	2	9	4	7	4	0	0
40.1 to 50	37	15	0	7	11	7	6	3	11	2	1	3
30.1 to 40	53	20	0	12	15	12	15	2	12	5	0	0
20.1 to 30	49	26	2	9	24	8	10	8	5	6	0	3
10.1 to 20	47	28	4	10	16	10	17	8	5	3	1	1
0.1 to 10	53	28	5	10	16	20	12	8	8	2	0	0
-9.9 to -0	44	32	3	9	22	17	8	6	7	4	0	0
-19.9 to -10	46	25	3	7	16	19	10	5	5	5	0	1
-29.9 to -20	11	15	2	6	5	2	6	2	0	2	1	0
-39.9 to -30	1	3	0	1	0	0	0	0	2	1	0	0
Totals	387	213	19	80	136	99	100	52	67	35	3	9

pressure so frequently encountered above this age, which are most often due to structural changes in the cardiovascular system. Observations on only three subjects above this age are included, one a hypothyroid man, and two women, both past 60, with typical exophthalmic goiter. A systolic pressure of 160 or over was arbitrarily set as the standard for exclusion from this series, except where a thyrotoxic patient with a high metabolic rate maintained such a pressure with no other evident cause. Electrocardiographic tracings were obtained in approximately two-thirds of the cases.

TABLE 2—*Averages of Pulse Rate, Pulse Pressure and Their Product in 600 Observations of the Basal Metabolic Rate*

	Basal Metabolic Rate											
	-39.9 to -30%	-29.9 to -20%	-19.9 to -10%	-9.9 to 0%	0.1 to 10%	10.1 to 20%	20.1 to 30%	30.1 to 40%	40.1 to 50%	50.1 to 60%	60.1 to 70%	70.1 to 80%
No. of observations	4	26	71	76	81	75	75	73	52	36	22	9
Mean pulse rate	59	61	64	71	72	78	81	93	100	104	108	114
Mean pulse pressure	28	32	35	41	43	45	49	51	58	59	69	81
Mean pulse rate × pulse pressure	1688	1987	2322	2867	3089	3482	4285	4892	5650	6521	7514	9171

Table 2 shows the data arranged according to the basal metabolic rate into classes, the class interval being made at each 10 per cent deviation from normal. It will be observed that the mean pulse rates increase as the metabolic rate increases. The same holds true for the pulse pressure. Chart 1 represents the facts recorded in this table. On this graph is also drawn the respective lines of regression for pulse rate and pulse pressure on basal metabolic rate. This line represents the ideal straight line which would be obtained from the averages of an enormous number of observations. In order to obtain this line it was necessary to calculate the coefficient of correlation between pulse rate and basal metabolic and between pulse pressure and metabolic rate. These figures were, respectively, 0.74 and 0.62. This coefficient is based on unity as

representing perfect correlation, and the figures obtained here would be interpreted as indicating that there is a marked correlation between both pulse rate and pulse pressure and metabolic rate, the relationship being somewhat closer for pulse rate than for pulse pressure

Table 2 gives only means for large groups and tells us nothing about individual cases, how closely the individual readings approximated the mean, or what the variation was within a group. An idea of this degree of variation is obtained from Table 3, which records the coefficients of variation for pulse rate and pulse pressure. It will be observed that pulse pressure is slightly more variable than pulse rate, that with seventy or more observations these values tend to be rather constant

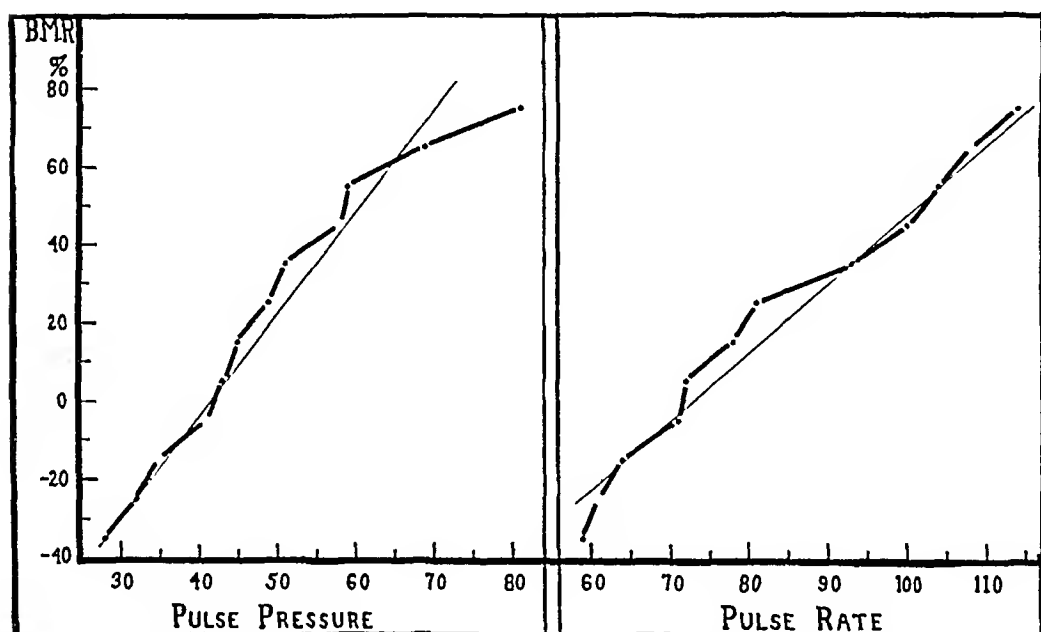


Chart 1—The dots, connected by the heavy line, represent the mean values for pulse pressure and pulse rate as they are affected by the basal metabolic rate. The data are in Table 2. The light, straight line is the line of regression for pulse pressure and pulse rate, respectively, on basal metabolic rate and is the best fitting straight line which can be drawn through the dots. It is the ideal "line of means."

and that with the higher metabolic rates the variability tends to increase.

Fluctuation in pulse rate and pulse pressure under the conditions of these observations is a significant fact and suggests further study. Several questions arise at once. Do all persons show a rise in both pulse rate and pulse pressure with elevated basal metabolic rate? Is the rise in each proportionate to the other and to the increase in rate? The first question may be answered by saying that no person was observed who did not show an increase in either pulse rate or pulse pressure with increased oxygen consumption. The answer to the second question would read that most individuals responded to increased oxygen con-



sumption with proportionate rises in pulse rate and pulse pressure, but some showed disproportionate rises in one or the other. For example, of two patients with basal metabolic rates of plus 34.6 per cent and 35 per cent, the former had a pulse rate of 102 while the latter's pulse rate was only 68, but their respective pulse pressures were 42 and 70 mm of mercury. Or again of two patients with metabolic rates of plus 67 per cent and 69 per cent, one had a pulse rate of 112 and pulse pressure of 48, while the pulse rate of the other was 85 with a pulse pressure of 94. These are extreme cases selected to illustrate the point under discussion, but this same phenomenon has been observed and commented upon by others.<sup>8</sup> There are many such cases in this series, in which the pulse rate was below its mean and the pulse pressure above its mean for that metabolic rate class, or vice versa. In other words, many individual cases were observed in which the deviations of pulse rate and pulse pressure from their respective means were in opposite directions.

TABLE 3—*Coefficients of Variation for Pulse Rate, Pulse Pressure and Their Product*

	Basal Metabolic Rate												
	—39.9	—29.9	—19.9	—9.9	0.1	10.1	20.1	30.1	40.1	50.1	60.1	70.1	
	to —30%	to —20%	to —10%	to 0.0%	to 10%	to 20%	to 30%	to 40%	to 50%	to 60%	to 70%	to 80%	
No. of observations	4	26	71	76	81	75	75	73	52	36	22	9	
Pulse rate	—	15.32	15.08	13.33	13.33	13.33	17.65	16.66	13.00	17.01	18.37	—	
Pulse pressure	—	31.25	21.85	20.73	17.74	20.88	24.08	29.21	22.88	30.67	22.53	—	
Pulse rate × pulse pressure	—	33.72	24.98	24.78	21.94	23.49	28.93	33.32	26.53	40.41	25.95	—	

These pulse rates and pulse pressure deviations in opposite directions from their means were of all degrees, but in 3.5 per cent of all observations their magnitude was 20 per cent or more from their respective means. This produced to a large extent the variability which is shown in Table 3. It is interesting to note that the coefficients here obtained correspond very closely with those obtained by Addis<sup>9</sup> in 300 normal persons.

It is a matter of interest to obtain the measure of the relationship between pulse rate and pulse pressure in this series. This is given by the coefficient of correlation between these two variables. It is noted from Table 4 that this is 0.489 and is positive, indicating that as pulse rate increases there is a decided tendency toward an elevation also in pulse pressure. This is the relationship as it exists in this series in which the basal metabolic rate is not constant but increases by 10 per cent at each

8 Sturgis, C. C. Observations on One Hundred and Ninety-Two Consecutive Days of the Basal Metabolism, Food Intake, Pulse Rate, and Body Weight in a Patient with Exophthalmic Goiter, *Arch. Int. Med.* **32**: 50 (July) 1923.  
9 Addis, Thomas. Blood Pressure and Pulse Rate Reactions, *Arch. Int. Med.* **30**: 240 (Aug.) 1922.

class interval It is possible to obtain a *partial* coefficient of correlation in which the factor of basal metabolic rate is held constant and its influence on pulse rate and pulse pressure eliminated This was done and the very low partial coefficient of correlation of 0.045 obtained, which indicates that there is practically no correlation between pulse rate and pulse pressure or, in other words, where there is a tendency for them both to increase in the same direction, this effect is neutralized by those instances where they vary in opposite directions If they all, or a majority, showed this tendency to vary in opposite directions, then the coefficient would be preceded by a negative sign, instead it has a positive sign but is almost zero

#### RECAPITULATION

We may recapitulate at this point by stating that both pulse rate and pulse pressure vary directly with the oxygen consumption, but the amount of variation in each is not always proportional but nevertheless there seems to be a compensating mechanism at work, for example, a disproportionate increase in pulse rate is compensated for by a relative decrease in pulse pressure or vice versa These observations suggest that a combination of pulse rate and pulse pressure would give a more correct estimate of the circulatory system's response to varying volumes of oxygen consumed than is afforded by either one alone An investigation of this point was undertaken and a conclusion reached after study and trial of various methods The two most feasible methods will be briefly discussed

#### PULSE RATE AND PULSE PRESSURE COMBINED

The first method which suggests itself is to combine pulse rate and pulse pressure by multiplying them together There is ample justification for this procedure, since the product of pulse rate by pulse pressure has been used by many investigators as a measure of the volume flow of blood and the study of this relationship has given rise to an extensive literature

Erlanger and Hooker<sup>10</sup> assumed that the pulse pressure represented the systolic output of the heart and, in 1904, utilized "the product of the pulse pressure by the pulse rate as an index to the relative velocity of blood flow" The "amplitude-frequency product" was also used by von Recklinghausen<sup>11</sup> in 1906, though it was probably first suggested by Hurthle in 1901 The pulse rate pulse pressure product has recently

10 Erlanger, J, and Hooker, D R An Experimental Study of Blood Pressure and of Pulse Pressure in Man, Johns Hopkins Hosp Rep **12** 145, 1904

11 Von Recklinghausen, H Was vir durch die Pulsdruckkreis & durch die Pulsdruckamplitude uber den grossen Kreislauf erfahren, Arch f exper Path u Pharmokol **56** 1, 1906-1907

been used by Addis,<sup>1</sup> who shows that in normal subjects the product increases under conditions, such as exercise, which call for increased volume flow of blood

More pertinent to the subject of this communication, however, are the observations of Murlin and Greer,<sup>12</sup> who report their work on dogs as well as on several men. They conclude "The results show a fairly close correlation in the same individual between the heart output expressed as the product of the pulse pressure and the heart rate on the one hand and the absorption of oxygen and the elimination of carbon dioxide on the other."

In this study the product in each individual observation was obtained and the means for each group calculated. These are recorded in Table 2. It was observed that the plotted line of these mean products was smoother than the mean lines for either pulse rate or pulse pressure. This was naturally to be expected since the small variations in either pulse pressure or pulse rate would tend to be equalized by variations in the opposite direction in the other factor. This was an advantage, and in individual instances accomplished the desired purpose of combining pulse rate and pulse pressure so as to get an expression which took cognizance of both, regardless of any variability in either. However, it also gave relative importance to each according to its numerical value, which was not desirable in all cases since we know that there is closer correlation between pulse rate and basal metabolic rate than there is between pulse pressure and metabolic rate.

There are two fundamental objections to the use of the product of pulse rate by pulse pressure. One is that it is more variable than either one of its components, as is demonstrated by the coefficient of variation shown in Table 3. This naturally results from the multiplication of small differences, which might be due to error, by large figures, 100 or more in some instances. Another objection to the product is that its use converts a linear relationship into one which is definitely non-linear. The line plotted from the mean products in Table 2 is definitely a curved line, whereas the lines of means for pulse rate and pulse pressure are apparently straight lines. This fact is also demonstrable statistically by employment of methods advanced by Blakeman,<sup>13</sup> the data for calculating which may be obtained from the statistical values obtained in this study and recorded in Table 4. By this test pulse rate is perfectly linear while pulse pressure shows only a slight tendency to

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12 Murlin, J. R. and Greer, J. R. The Heart Action in Relation to the Respiratory Metabolism, *Proc. Am. Physiol. Soc.*, **18**, 1910, *Am. J. Physiol.* **27** 1910-1911.

13 Blakeman, J. On Tests for Linearity of Regression in Frequency Distributions, *Biometrika* **4** 332, 1905.

deviate from linearity The nonlinearity of the product of pulse rate and pulse pressure is confirmed by this test

There is one further objection to the utilization of the product as a means of combining the two variables, pulse rate and pulse pressure It has come to represent a rough measure of the volume flow of blood, the pulse rate indicating the rate of flow and the pulse pressure the systolic output of the heart There is no objection to assuming that the rate of heart beat influences rate of blood flow, but many careful investigators claim that pulse pressure is not an indication of systolic cardiac output and Yandell Henderson, who is supported by Haldane, maintains that the systolic cardiac output is a constant and is so maintained under a variety of conditions On the other hand, Means and Newburgh<sup>14</sup> have shown that an increase in the systolic output may be a factor in increasing the volume flow of blood These investigators remark in

TABLE 4—*Statistical Values and Relationships*

Symbol	M	$\sigma$ (sigma)	$\rho$ (rho)		$\eta$ (eta)	$\zeta$ (zeta)
Designation						
	Mean	Standard Devia-	Coefficient of Correlation		Correlation Ratio With Basal Metabolic Rate	$\eta^2 - \rho^2$
		tion	With Basal Metabolic Rate	With Pulse Pressure		
Basal metabolic rate (0)	16.9	25.2				
Pulse rate (1)	82.4	19.3	$0.745 \pm 0.013$	0.489	0.745	0
Pulse pressure (2)	47.9	15.5	$0.625 \pm 0.015$		0.633	$0.01006 \pm 0.0055$
Pulse rate $\times$ pulse pressure	4020	2060	$0.759 \pm 0.012$		0.804	$0.07033 \pm 0.0145$

discussing one of their subjects "Up to 700 kilogram-meters of work per minute the increase in blood flow was met chiefly by an increase in the volume per beat, beyond that point by an increase in the pulse rate" It must be remembered that they were measuring the systolic output of the heart by an objective method, which lends support to the assumption that changes in pulse pressure indicate variations in the systolic output of the heart

That variations in pulse pressure as well as pulse rate occur, and that there seems to be some regularity in their occurrence is quite apparent from this and other studies But, since these variations, though they appear to be purposeful, are not thoroughly understood, it was considered advisable to treat them in an abstract manner simply as variables and combine them in the manner that seemed most expedient irrespective of any theory or interpretation as to their significance

It has been mentioned that the coefficient of correlation between pulse rate and basal metabolic rate was 0.74, and the coefficient for pulse pres-

<sup>14</sup> Means, J. H., and Newburgh, L. H. Studies of the Blood Flow by the Method of Krogh and Lindhard, *Tr. A. Am. Phys.* **30**: 51, 1915

sure and metabolic rate was 0.62. It is possible to calculate a multiple coefficient of correlation which utilizes the relationships existing between pulse rate, pulse pressure and basal metabolic rate and also between pulse rate and pulse pressure themselves. This was done and a multiple coefficient of correlation of 0.80 was obtained. This is appreciably higher than the coefficient of correlation for pulse rate or pulse pressure alone, and may be taken as an indication of the advantage to be gained by combining the values for these two functions.

In a previous communication<sup>15</sup> on this subject, a doubt was expressed as to whether the relationship existing between basal metabolic rate and pulse rate combined with pulse pressure was truly linear or curvilinear. From further study with twice the number of observations it now becomes apparent that a straight line most nearly represents the facts. Such a straight line may be obtained by utilization of the relationships which are revealed by a statistical analysis of these data. The values are all contained in Table 4 and may be substituted in the following equation:

$$1 \quad \chi_0 = \left[ \beta_{01 \cdot 2} \frac{\sigma_0}{\sigma_1} \right] \chi_1 + \left[ \beta_{02 \cdot 1} \frac{\sigma_0}{\sigma_2} \right] \chi_2 + \left[ M_0 - \beta_{01 \cdot 2} \frac{\sigma_0}{\sigma_1} M_1 - \beta_{02 \cdot 1} \frac{\sigma_0}{\sigma_2} M_2 \right]$$

$$\text{In which } \beta_{01 \cdot 2} = \frac{r_{01} - r_{02} r_{12}}{1 - r_{12}^2} \text{ and } \beta_{02 \cdot 1} = \frac{r_{02} - r_{01} r_{12}}{1 - r_{12}^2}$$

Substituting the values and reducing to its simplest form this equation becomes:

$$2 \quad \text{B M R} = 0.75 (\text{P R} + 0.74 \text{ P P}) - 72$$

From such an equation a straight line may be plotted which represents the relationship between basal metabolic rate on the one hand and pulse rate and pulse pressure on the other. This line has been drawn in Chart 2 and on it have been placed the 600 observations of pulse rate and pulse, pressure from whose values and relationships the line is derived.

Careful inspection of Chart 2 suggests the possibility that a curved line could be drawn through the dots which would more nearly pass through the areas of their greatest concentration. In order to ascertain this point with certainty the means of the columns 70-80, 80-90, etc., in Chart 2 were obtained and are placed as crosses on this graph with the best fitting curve drawn through them. It becomes evident from inspection of these lines that in the metabolic rate classes above plus 20 per cent there is a tendency for the means to deviate from the straight line. This same tendency toward a wider divergence in the readings

<sup>15</sup> Read, J. M. Correlation of Basal Metabolic Rate with Pulse Rate and Pulse Pressure, J. A. M. A. 78:1887 (June 17) 1922.

obtained from patients with the higher basal metabolic rates is noted in the coefficients of variation (Table 3), which increase in magnitude with the higher metabolic rates. This point is shown graphically by the increased scatter of the dots in the upper part of Chart 2.

In view of the marked linearity in the relationship between pulse rate and pressure and basal metabolic rate, with rates up to plus 20 per cent, it would seem pertinent to inquire for a cause of the deviation from linearity noted with the higher metabolic rates. There is especially noted a tendency, beginning at about plus 55 per cent, for the combined

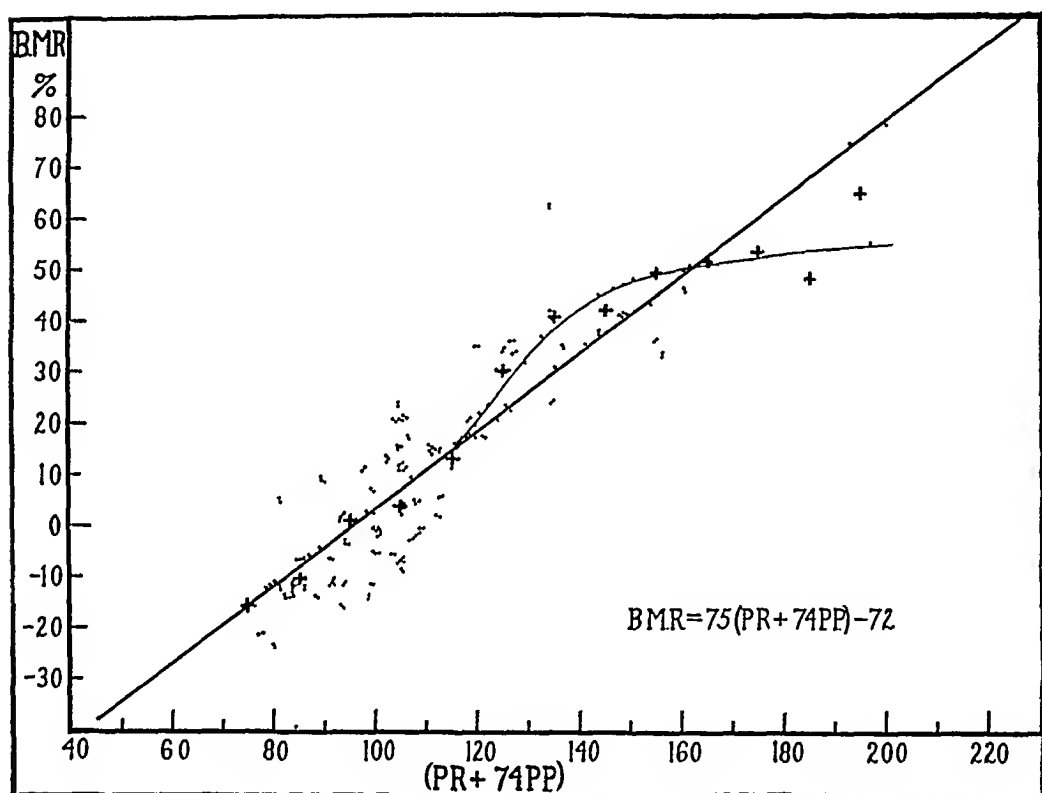


Chart 2—The heavy straight line is the line of regression for combined pulse rate and pulse pressure on basal metabolic rate and is represented by the equation  $BMR = 0.75 (PR + 0.74 PP) - 72$ . The 600 dots represent the individual observations from whose values and relationships the line was derived. The crosses are the means of the columns, and the curved line passing through them in the upper portion illustrates the extent of the tendency for pulse rate and pulse pressure to deviate from linearity when the metabolic rate is above plus 20 per cent. It is also to be observed that above this point there is greater variability, as evidenced by the increased scatter of the dots.

pulse rate and pulse pressure figures to increase out of all proportion to increase in the basal metabolic rate. The patients with these higher metabolic rates were all suffering from so-called hyperthyroidism and in this fact probably lies the cause of the observed phenomenon. Cardiac decompensation, however, is not a factor, as no thyrotoxic patients with

myocardial failure or auricular fibrillation are included in this series. It seems more probable that factors inherent to the disease itself are operating to cause the changes noted.

The apparently ineffectual increase of the work of the circulatory system when the metabolic rate becomes high brings to mind a recent report by Plummer and Boothby,<sup>16</sup> in which they showed that patients with exophthalmic goiter were very inefficient as machines, such patients expending about twice as much energy as normal persons doing the same work. All these facts taken together would seem to indicate that exophthalmic goiter is not simply hyperthyroidism. If it were, the same linear relationship should hold for the higher metabolic rates as holds for rates obtained from normal and hypothyroid subjects. When thyrotoxic patients are the subjects there may be, and probably are, other factors which are operating to increase the pulse rate, namely, toxemia and, perhaps, increased sympathetic instability. These factors also affect blood pressure but in a manner more difficult to appraise. Inspection of Table 3 and Chart 2 certainly reveals wider variability in pulse rate and pulse pressure with increasing metabolic rate.

#### PRACTICAL APPLICATIONS

It has been suggested<sup>17</sup> that the resting pulse rate be utilized as an index of the basal metabolic rate. Means and Aub<sup>18</sup> found that in about 60 per cent of cases studied by them "there is a close parallelism between pulse and metabolism, and in the remainder a certain amount of parallelism." They further state "The pulse rate, however, gives comparative results only, for between metabolism elevation of different persons there seems to be but little relationship. The pulse rate, therefore, is not an index of the absolute degree of intoxication in the patient seen at different times." These statements concerning pulse rate are equally true of pulse pressure. Hence it follows that if an index of basal metabolic rate is sought, the value of such index is enhanced by utilization of pulse pressure as well as pulse rate. First the best means of combining these values must be decided. Although a curved line seems to fit best the data here reported, still there is the difficulty that a formula representing such a line becomes too complicated for practical use. This same result could be obtained by utilizing Chart 2 directly, and noting the relation of the dot obtained to the curved line of the means. Because of its simpler application, however, the linear formula is suggested as

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16 Plummer, H. S., and Boothby, W. M. The Cost of Work in Exophthalmic Goiter, *Am J Physiol* **63** 406-407 (Feb.) 1923.

17 The Pulse Rate in Relation to Metabolism and Diagnosis, Editorial, *J. A. M. A.* **76** 181 (Jan. 15) 1921.

18 Means, J. H., and Aub, J. C. The Basal Metabolism in Exophthalmic Goiter, *Arch Int Med* **24** 645 (Dec.) 1919.

the most useful for clinical work if a prediction formula is desired. So by substituting pulse rate and pulse pressure readings in the foregoing equation (2) an estimation of the basal metabolic rate may thereby be obtained. Inspection of Chart 2 shows that only a little over half of the observations would fall within 10 per cent above or below the correct value. This is no objection, however, to utilization of pulse rate and pulse pressure as a rough guide in following the course of a hypothyroid or thyrotoxic patient who is under treatment. The reliability of the figures becomes greatly enhanced by obtaining them at an examination, simultaneously with an estimation of the basal metabolic rate and thus establishing the relationship which exists *in that person* between pulse rate, pulse pressure and basal metabolic rate. When the pulse rate and blood pressure are obtained under the same basal conditions necessary for satisfactorily determining a basal metabolic rate these values would seem to be sufficiently reliable to warrant their use where it is not practical to obtain frequent determinations of the basal metabolic rate.

#### CONCLUSIONS

1 Pulse rate varies directly with the basal metabolic rate, the coefficient of correlation between pulse rate and basal metabolic rate being 0.74.

2 Pulse pressure also varies directly with the basal metabolic rate, the coefficient of correlation in this case being 0.62.

3 Since different persons vary in the amount of change in either pulse rate or pulse pressure, a more reliable measure of the circulatory system's response to variations in oxygen consumption is a combination of pulse rate and pulse pressure in the manner suggested below.

4 Pulse rate and pulse pressure changes may be utilized as a rough guide to changes in a patient's basal metabolic rate, particularly becoming more reliable if the relationship to metabolic rate is once established by obtaining all the basal figures simultaneously. By substituting the basal pulse rate and pulse pressure readings obtained in any given case in the following formula, an estimate of the basal metabolic rate may be obtained.

$$B M R = 0.75 (P R + 0.74 P P) - 72$$

This will give the basal metabolic rate within 10 per cent of its correct value in slightly over half of the cases.



# THE ALLEGED RÔLE OF LACTIC ACID IN ARTHRITIS AND RHEUMATOID CONDITIONS \*

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In 1858 Richardson<sup>1</sup> published the results of extensive experiments on dogs in which the injection of large quantities of lactic acid, intraperitoneally, was followed by severe joint involvement. The condition of the joints was similar to that seen in acute arthritis, and Richardson suggested that the arthritic syndrome was due to an accumulation of lactic acid in the body. This theory found further support in 1877, when Foster<sup>2</sup> reported that the administration of lactic acid by mouth to two diabetic patients resulted in painful and swollen joints. The pain and swelling persisted as long as the lactic acid administration was continued and disappeared promptly after the acid was discontinued. These early experiments were apparently never repeated or extended but they have exerted some influence in the formation of hypotheses regarding the disease. Within very recent years, for example, the theory that arthritis and muscular rheumatism are characterized by an excessive accumulation of lactic acid in the body has been revived, chiefly on clinical grounds, by Wilde, and has found expression in his book on arthritis<sup>3</sup>.

Moreover, in view of the known relation of lactic acid to muscular contraction and rigor mortis, and in view of the peculiar dysfunction characteristic of rheumatic myositis and the beneficial influence on it of passive motion, massage and active motion, there has been ample basis on which to erect an hypothesis correlating the disease process with a disturbed production or removal of lactic acid. It is conceivable that if such a disturbance exists there would be a reasonable probability of detecting it by a determination of the lactic acid in the blood and other body fluids.

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\* From the Laboratory of Clinical Chemistry, Presbyterian Hospital. The work here reported is part of a study on chronic arthritis in collaboration with Robert B Osgood, M D, of Boston. The expenses of the investigation were defrayed by contributions from several sources, including a number of patients.

1 Richardson, B W. The Cause of the Coagulation of the Blood. The Astley Cooper Prize Essay for 1856, London, John Churchill, 1858, Appendix III, p 371.

2 Foster, B. Clinical Medicine, London, J and A Churchill, 1874, p 143.

3 Wilde, P. Physiology of Gout, Rheumatism and Arthritis, New York, William Wood & Co, 1922.

According to the present conception of the physiologic significance of lactic acid, excessive production of this acid or faulty removal of it from the body would indicate marked abnormal oxidative function, either in respect to intermediary glucose metabolism or to products of the energy transformation in muscular and perhaps glandular activity. In order to ascertain whether there occurs in arthritis such deviation from normal physiology as is implied by the lactic acid theory, it has seemed desirable to test this theory by chemical determination of the quantities of lactic acid present in the body fluids of arthritic patients and normal persons. Methods for the determination of lactic acid are at present available whereby the lactic acid present in small amounts of biologic material can be quantitatively evaluated with a fair degree of accuracy.

#### EXPERIMENTAL

Persons suffering from acute or chronic arthritis were used as subjects in this investigation. Both proliferative and degenerative types with widely varying degrees of involvement and disability were represented in this group. The normal subjects were drawn from convalescent surgical cases and various hospital workers who apparently were in good health. Venous blood samples were drawn from the cubital vein usually in the post-absorptive period and always after a period when excessive muscular activity had been avoided. The urine analyses were made on twenty-four hour samples, and on samples voided before and after exposure to external heat. Sweat samples were collected in a rubber bag surrounding the forearm during a general sweat induced by an electric "baker." The skin of the arm and hand was cleaned with water, alcohol and ether before inserting the limb into the bag. One sample of nonseptic joint fluid was obtained by aspiration from an arthritic knee joint.

For the determination of lactic acid Clausen's method has been used.<sup>4</sup> This method has proved fairly satisfactory in our hands. Using a metal alloy bath and sulphuric acid to decompose the lactic acid to acetaldehyd it was possible to recover an average of 94 per cent of the lactic acid contained in lithium lactate solutions and about the same proportion of lactic acid added to blood. The use of traps to avoid mechanical passage of droplets from the reaction tube to the bisulphite solution and the maintenance of the latter at a  $p_H$  of 3.0 to 5.5 are details that Clausen has suggested as contributory towards uniform results.<sup>5</sup>

Clausen's directions have been followed in the treatment and analysis of blood and urine. Sweat samples have been prepared for analysis by precipitating the small amount of protein present with

4 Clausen, S.W. J Biol Chem 52 263 (May) 1922

5 Personal Communication

tungstic acid in the manner customary for blood proteins. In none of the sweat samples that we tested have reducing sugars been found and, consequently, the preliminary removal of glucose, necessary with blood filtrates, was dispensed with. Nearly identical results for lactic acid were obtained from tungstic acid filtrates prepared in this way and from ether extracts of sweat.

### RESULTS AND DISCUSSION

As will be seen from Table 1, the content of lactic acid in the venous blood of arthritic patients is quantitatively similar to the blood content of lactic acid of normal persons. These figures are of the same magni-

TABLE 1—*Lactic Acid Content of Whole Blood*

Name	Diagnosis †	Lactic Acid, Mg per 100 C c	Remarks
*Sh e	Proliferative arthritis	23	
*L s	Arthritis	21	After 10 gr. acetylsalicylic acid
*Fl l	Proliferative arthritis	20	After 10 units insulin
*Fl l	Proliferative arthritis	16	After 10 units insulin
*A s r	Proliferative arthritis	26	
St n	Proliferative arthritis	26	
*Sch d	Degenerative arthritis	19	
*D n d	Degenerative arthritis ?	17	
*D n d	Degenerative arthritis ?	18	After "bake"
P t r	Subacute rheumatic fever	11	
V-s	Proliferative arthritis	23	
V s	Proliferative arthritis	22	
*G-y e	Proliferative arthritis ?	25	
D l p	Psoriasis and diabetes	30	
K g-e	Arthritis	19	
O i	Normal	20	
O l l	Proliferative arthritis	21	
O l l	Proliferative arthritis	19	
Cr t r	Normal	16	
C-r l l	Malignant tumor of liver	16	
O i	Normal	20	

† An attempt was made to classify the arthritic patients studied, according to the classification of Nichols and Richardson, into the proliferative and degenerative types but this was not always clinically possible. Practically all subjects presented some symptoms of rheumatic myositis. This was conspicuous in the cases starred.

tude as reported by other investigators. Clausen finds a lactic acid range of from 15 to 32 mg per hundred cubic centimeters in convalescent children at rest in bed. Barr, Himwich and Green,<sup>6</sup> using Clausen's method, found from 14 to 25 mg lactic acid in arterial blood of resting persons. After three minutes exercise the lactic acid in the blood of these same persons rose to levels from three to five times higher than the resting level. These experiments, just cited, demonstrate clearly that excessive production of lactic acid, in muscle tissue at least, is promptly reflected in the blood, and it is difficult to escape the conclusion that if there is excessive production of lactic acid in the course of the arthritic or rheumatic process it would be revealed in abnormally high

<sup>6</sup> Barr, D. P., Himwich, H. E., and Green, R. P. J. Biol. Chem. **55**: 495, 1923.

values in the circulating blood. It is of interest, perhaps, to note that the lowest blood lactic acid recorded in Table 1 was from a case of non-febrile acute rheumatism where muscular movement probably was at a minimum because of the extreme pain involved. A value of 28 mg of lactic acid per hundred cubic centimeters of fluid was obtained in the one sample of nonseptic joint fluid studied.

In Table 2 are given a few determinations of lactic acid in urine. We have been unable to obtain residues from ether extracts of urine that did not char considerably in the reaction tube with sulphuric acid, and we are unwilling to place much reliance on the figures as representing

TABLE 2—*Urinary Excretions of Lactic Acid and Organic Acids in Arthritis*

Name	Total Volumes, Cc	Hourly Volume, Cc	$pH$	Lactic Acid Mg per 100 Cc	Lactic Acid Mg per Hour	Organic Acids Cc of 0.1 N per Hour	Remarks
Sh-e	62	53.1	6.8	18	9	6.4	Before "bake"
Sh-e	58	69.6	6.8	20	14	7.7	After "bake"
Sh-e	1,250	52.1	6.4	15	8	18.0	24 hour sample
Sh-e	1,180	49.2	6.2	26	13	15.3	24 hour sample day of "bake"
Sh-e	1,200	53.8	6.2	11	6	19.3	24 hour sample
L-s	1,805	75.2	6.8	8	6	21.8	24 hour sample
L-s	1,058	44.1	6.0	13	6	17.9	24 hour sample day of "bake"
L-s	765	31.9	7.8	18	6	21.0	24 hour sample
S-ch	35	30.0	5.6	14	4	13.5	Before "bake"
S-ch	24	22.2	5.6	15	3	10.0	After "bake"
H-r	134	89.3	5.6	23	21	25.5	Before "bake"
H-r	102	72.0	7.2	21	15	30.2	After "bake"
H-r	61	52.2	5.8	31	16	31.8	Before "bake"
H-r	110	62.8	6.6	22	14	35.8	After "bake"
B-s	1,873	78.0				12.6	24 hour sample
B-s	1,840	76.7				14.4	24 hour sample
B-s	2,305	96.0				18.3	24 hour sample
C-t-n	1,320	55.0				11.8	24 hour sample
C-t-n	1,625	67.7				14.2	24 hour sample
A-r-n	1,210	50.4				11.5	24 hour sample
A-r-n	1,565	65.2				11.9	24 hour sample
S-p-d	1,150	47.9	5.4			15.1	24 hour sample
S-p-d	1,410	58.8	6.2			17.1	24 hour sample
S-p-d	1,370	52.9	6.0			14.0	24 hour sample
S-p-d	975	40.6	6.4			16.4	24 hour sample

lactic acid alone. However, there is no indication of excessive amounts of bisulphite binding compounds in these ether extracts. The excretion of large amounts of lactic acid in urine would be revealed in the titration for organic acids as carried out by the procedure of Van Slyke and Palmer.<sup>7</sup> These authors have shown that lactic acid is titrated to an extent of 93 per cent in their method. Many titrations for organic acids have been made in arthritic urines without finding abnormally high values. Some of these results are included in Table 2.

Particular attention has been paid to the sweat since Wilde ascribes the value of sweating measures in arthritis largely to the elimination of lactic acid in the sweat. As will be seen from Tables 3 and 4 considerable quantities of lactic acid were found in sweat, but the sweat of arthritic patients contained no more than the sweat of normal persons.

7 Van Slyke, D. D., and Palmer, W. W. *J. Biol. Chem.* **41**: 567 (April) 1920.

The quantity of lactic acid present in the sweat of both groups varies over a wide range and the concentration in any sample seems dependent on the dilution of the sweat. The water content of sweat increased

TABLE 3—*Lactic Acid Content of Arthritic and Normal Sweat*

Name	Diagnosis	pH	Lactic Acid Mg per 100 C c	Total Solids, per Cent	Ash, per Cent
M-n (a)*	Normal	6.6	287	1.32	0.88
(b)*		7.8	120	0.85	0.79
O (a)	Normal	7.4	186	1.13	0.81
(b)		7.6	136	1.01	0.83
P t n (a)	Normal	4.8	350	1.19	0.39
(b)		6.4	171	0.73	0.61
P c (a)	Arthritis	6.2	234	1.17	0.62
(b)		6.5	145	0.90	0.66
M l n (a)	Arthritis	6.0	458	1.49	0.61
(b)		6.0		1.07	
Sch d (a)	Arthritis	7.2	206	0.93	0.71
(b)		7.4	148	0.74	0.64
Ar t	Normal	6.6	166		
A n	Normal		248		
M-ll	Normal		424		
H-n n	Arthritis	6.4	196		
G s	Arthritis	6.8	139		
M-t-f	Arthritis	6.8	104		
W-e	Nephritis	5.8	212		
R ph	Psoriasis	5.4	130		
F s	Arthritis	5.8	200		
S-ck	Arthritis	6.0	184		
Sh e	Arthritis	6.9	164		
L-s	Arthritis	6.4	326		
K l r	Arthritis	5.2	220		
D-n d	Arthritis	6.8	207		
F ty	Arthritis	6.1	208		

\* (a) and (b) refer respectively to sweat samples taken early and late in the course of the electric "bake."

TABLE 4—*Lactic Acid and Total Organic Acid Content of Arthritic Sweat*

Name	Diagnosis	pH	Lactic Acid Mg per 100 C c	Lactic Acid C c of 0.1 N per 100 C c	Organic Acids C c of 0.1 N per 100 C c	Per Cent Organic Acids as Lactic Acid
S ck	Arthritis	6.0	184	20	35	57
D n d	Arthritis	6.8	207	23	34	78
D n-d	Arthritis	6.5	230	26	40	65
R-t r	Arthritis and psoriasis	6.8	149	17	27	63
R-t-r	Arthritis and psoriasis	5.6	98	11	23	48
R-t-r	Arthritis and psoriasis	6.8	186	21	31	68
R-t r	Arthritis and psoriasis	7.0	159	18	31	58
R-t r	Arthritis and psoriasis	6.6	250	28	50	56
R-t r	Arthritis and psoriasis	7.0	151	17	52	33
R-t r	Arthritis and psoriasis	7.0	146	16	34	47
Sch d	Arthritis	7.0	126	14	27	52
Sch d	Arthritis	6.8	136	15	21	71
Sch d	Arthritis		113	13	52	25
Sch d	Arthritis		90	10	39	24
M t f	Arthritis	6.6	131	15	25	60

appreciably as the individual continued to sweat. The diminution of solids seems to be largely a loss of the organic solids. Little change in the ash concentration was found, though occasionally an increase in late samples. This is in keeping with the observation of Adolph<sup>8</sup> that

the chlorid content of sweat increases during sweating, reaching a plateau after from twenty to thirty minutes of sweating. The figures for the ash content of sweat are considerably higher than the recently published results of Talbert<sup>9</sup>. The range of lactic acid figures found for arthritic patients and normal persons, and given in the various tables, are summarized as follows:

Arthritis patients    Blood, from 11 to 30 mg per hundred cubic centimeters  
Urine, from 3 to 21 mg per hour, from 8 to 31 mg per hundred cubic centimeters  
Sweat, from 90 to 458 mg per hundred cubic centimeters

Normal persons    Blood, from 14 to 25 mg per hundred cubic centimeters,  
from 15 to 32 mg per hundred cubic centimeters    Barr, Hinwisch and Green,<sup>9</sup>  
Clausen<sup>4</sup>    Urine, from 5 to 13 mg per hundred cubic centimeters    Sweat,  
from 120 to 424 mg per hundred cubic centimeters

In a number of cases when large quantities of sweat were available, an approximation of the total organic acid content was obtained by titration. Van Slyke and Palmer's procedure for organic acids in urine was used,<sup>7</sup> and the titration carried out on 10 c c samples of sweat. The results, given in Table 4, indicate that lactic acid makes up about one half of the total organic acids contained in sweat.

As early as 1852, Favre<sup>10</sup> isolated the zinc salt of lactic acid and identified lactic acid as a sweat constituent. Ryffel,<sup>11</sup> as a result of one analysis by his own method, also reported its presence in sweat collected during a Turkish bath. Clausen has emphasized the fact that his method is not specific for lactic acid and in order to satisfy ourselves that we were actually dealing with lactic acid in appreciable amounts, large quantities of acidified sweat were extracted with ether and lactic acid was isolated from it as zinc lactate. By analysis of this zinc salt, the lactic acid in sweat was identified as *d*-lactic acid. The yield was about 50 per cent of the amount indicated by Clausen's method as being present.

0.1062 gm substance after drying to constant weight at 105 C weighed 0.0925 gm

0.0402 gm anhydrous substance gave 0.0137 gm zinc oxid (ZnO)

0.0244 gm anhydrous substance gave 0.0083 gm zinc oxid (ZnO)

0.1936 gm in 14.23 gm water in 20 cm tube  $\alpha = -0.3$  degrees

Calc for  $\text{Zn}(\text{C}_3\text{H}_5\text{O}_3)_2 \cdot 2\text{H}_2\text{O}$ , water = 12.88 per cent

Found water = 12.90 per cent

Calc for  $\text{Zn}(\text{C}_3\text{H}_5\text{O}_3)_2$  zinc oxid = 33.43 per cent

Found zinc oxid = 34.08, 34.02 per cent

( $\alpha$ )  $D^{20}_D = -11.1$  ( $c = 1.25$  per cent) (Beilstein, 3 263, 1921)

Found ( $\alpha$ )  $D^{20}_D = -11.0$  ( $c = 1.36$  per cent)

<sup>9</sup> Talbert, G. A. Am J Physiol **63** 350 (Jan) 1923

<sup>10</sup> Favre, M. P. A. Compt rend Acad d sc **35** 721, 1852

<sup>11</sup> Ryffel, J. H. J Physiol **39** 29, 1910

The presence of lactic acid as a sweat constituent and its occurrence there in concentrations much greater than are ordinarily found in blood, suggests that it is a product of chemical changes occurring in the sweat glands during secretion. Presumably it is an expression of the energy changes performed by the sweat glands in elaborating the typical secretion in a manner analogous to lactic acid formation during muscular work.

#### SUMMARY

1 The lactic acid contents of the blood, urine and sweat of patients suffering from arthritis and rheumatic disabilities has been determined and the results have been compared with the respective lactic acid contents from nonarthritic persons. The lactic acid was determined also in the synovial fluid from a case of joint effusion. In no case have we observed abnormal quantities of lactic acid in the arthritic patients. These findings therefore lend no support to the idea that arthritis, at least of the types studied, is caused or characterized by abnormal production or disposal of lactic acid.

2 Lactic acid has been found to be present in sweat in considerable quantities, making up about 50 per cent of the organic acids of sweat. Its presence in this secretion may be referable to the chemical changes occurring in the sweat glands during their activity.

3 The benefit accruing to arthritic patients from sweating measures cannot, in the light of these results, be ascribed to the elimination of lactic acid in the sweat.

# STUDIES ON THE METABOLISM OF OBESITY

## III THE SPECIFIC DYNAMIC ACTION OF FOOD \*

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The first line of experimentation followed by us in our studies on the metabolism of obesity was directed toward the possible discovery of variations in the specific dynamic action of foods in persons of widely different body build. In 1921 one of us <sup>1</sup> reported our first experiments on the specific dynamic action of carbohydrate. No definite conclusions were drawn from this study. The work has subsequently been extended, until at the present time we are able to report the original series of experiments on carbohydrate utilization performed with the Benedict portable respiration apparatus, and a larger series done with the Tissot gasometer in which carbohydrate, protein and fat meals were studied.

When our work was first started, no very definite experimental data were available on variations in the specific dynamic action of foods. In the large series of cases studied by Benedict and Carpenter <sup>2</sup> no attention was paid in the protocols to the question of body weight. We attempted to correlate changes in the metabolism following food ingestion with original differences in the height-weight proportions of their subjects, but our analysis yielded nothing definite. In our first communication we, however, had expressed the opinion that, since up to that time no one had been able to explain obesity on the basis of variations in basal metabolism, a theoretical explanation might be found in one of two ways: (a) an unusual use of food stuffs, (b) variation in energy expense by different persons performing the same task. The conception that foodstuffs are not necessarily metabolized in the same way by all persons implied individual variations in the so-called specific

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\* From the Medical Clinic, the Gusta Morris Rothschild Fund and the Otto Baer Fund for Clinical Research of the Michael Reese Hospital and the Nelson Morris Memorial Institute for Medical Research.

1 Strouse, Solomon. Carbohydrate Oxidation in Relation to Body Weight, American Soc. for Clinical Investigation, May 5, 1921, Chicago, American Medical Association, 1921.

2 Benedict, F G, and Carpenter, T M. Food Ingestion and Energy Transformations, Publication No. 261, Carnegie Institution of Washington, 1918.



dynamic action of food. Other phases of the problem have been discussed in previous papers of this series<sup>3</sup>

Although in the earlier literature numerous opinions are found concerning "slowing of metabolism" in obesity, incontrovertible experimental evidence is scant. The original report of Jaquet and Svenson,<sup>4</sup> of which we were not aware at the beginning of our research, contains a study of three cases of obesity, all of which showed normal basal metabolism. These three persons were given meat and mixed food, and the effect on the metabolism measured. The increases were compared with those found by Magnus-Levy<sup>5</sup> in 1893, and the authors state that "the increase in oxidation after food was significantly less and of shorter duration than with normals." In a matter so important for the understanding of a fundamental problem in metabolism, it seems fair to suggest in criticism of this work that the absence of normal standards of their own lessens the value of their conclusions.

No further experiments are available until 1915, when Means<sup>6</sup> studied the effect of glucose and of meat on the metabolism of one case of obesity. He concluded that "the specific dynamic action of protein is as great in this case of obesity as in normal individuals." Means used no normal controls and compared his results with the normal figures obtained by Gigon.<sup>7</sup> Of comparative interest perhaps is the contribution of Rabe and Plaut,<sup>8</sup> who found a diminished specific dynamic action of protein in a person accustomed to low nitrogen diet. Rolly<sup>9</sup> had a rare opportunity of studying specific dynamic action in obesity. One patient with tuberculosis of the testicle was studied before and after castration. His weight before castration was 56.7 kg and some time after the operation was 86.1 kg. The specific dynamic action of protein was very high during the first period, and much lower when the patient became obese. This author also studied a woman with exophthalmic goiter who, after thyroidectomy and pregnancy, increased in weight from 57 kg to 89.5 kg. The results were the same as in his first case. When, however, this woman was given thyroid

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3 Strouse, Solomon, Wang, C. C., and Dye, Marie. Studies on the Metabolism of Obesity, *Arch Int Med* **34** 275 (Sept.) 1924.

4 Jaquet, A., and Svenson, N. Zur Kenntnis des Stoffwechsels fettsuchtiger Individuen, *Ztschr f klin Med* **41** 375, 1900.

5 Magnus-Levy, A. Ueber die Grosse des respiratorischen Gaswechsels unter dem einfluss der Nahrungsaufnahme, *Arch f d ges Physiol* **55** 1, 1893.

6 Means, James H. Studies of the Basal Metabolism in Obesity and Pituitary Disease, *J M Res* **32** 121, 1915.

7 Gigon, A. Ueber den Einfluss der Nahrungsaufnahme auf den Gaswechsel und Energieumsatz, *Arch f d ges Physiol* **140** 509, 1911.

8 Rabe, F., and Plaut, R. Zur Frage eiweissarmer Ernährung, *Deutsch Arch f klin Med* **137** 187 (Aug.) 1921.

9 Rolly, F. Zum Stoffwechsel bei der Fettsucht, *Deutsch med Wchnschr* **47** 887 (Aug 4) 1921.

extract therapeutically, the specific dynamic action of protein again rose. Although Rolly believes that his experiments suggest lowered specific dynamic action as a factor in producing obesity, it is evident that patients with tuberculosis and exophthalmic goiter are not suitable as "normal controls" and his experimental results cannot be accepted as conclusive.

In 1922 Plaut<sup>10</sup> published the results of an investigation of a large series of persons, normal and abnormal, on whom the specific dynamic action of a mixed meal was studied. This is the first published report on obesity of which we are aware, in which the investigator determined his own "normals." Plaut used the Benedict portable apparatus with standard technic. After basal metabolism was determined, a meal composed of 200 gm of chopped beef, 50 gm fat, 200 gm bread and 500 c c coffee was given. In one hour the increase in oxygen consumption was again determined.

In well nourished persons Plaut found an increase of from 24 to 30 per cent in the metabolism. Three stout, otherwise healthy persons showed the same increase. Forty-two abnormal persons were studied. Some of the author's results are found in Table 1.

TABLE 1—*Specific Dynamic Action of Mixed Meal*

	Number of Cases	Percentage Increase
Normal persons	19	20 to 50
Constitutional obesity	12	4 to 29
Hypophyseal obesity	10	—3 to 18
"Constitutional thinness"	3	63, 40, 48 respectively

It will be seen that Plaut found a very definite lowering of the specific dynamic action of food in cases of obesity, and a very marked rise in the opposite type of persons, those with so-called "constitutional thinness." These experiments lasted only for one hour.

The following year Plaut<sup>11</sup> added twenty-six new cases to her first series with the same conclusions.

Liebesny<sup>12</sup> reported some excellent work on ten normal persons and sixty-one cases of obesity, complicated with endocrine disturbances. His test meal consisted of 200 gm of roast veal and 100 gm of bread. Basal metabolism was determined on each patient, and readings were taken one hour, one and a half hours, and sometimes two hours after the meal. He divided his cases into five groups on the basis of variation in metabolism and variation in specific dynamic action of protein,

10 Plaut, Rahel. Gaswechseluntersuchungen bei Fettsucht und Hypophysiserkrankungen, *Deutsch Arch f klin Med* **139** 285 (May) 1922.

11 Plaut, Rahel. Gaswechseluntersuchungen bei Fettsucht, II, Mittheilung, *Deutsch Arch f klin Med* **142** 266 (June) 1923.

12 Liebesny, P. Die Zpezifisch-dynamische Eiweisswirkung, *Biochem Ztschr* **144** 308, 1924.

emphasizing particularly these conditions as affected by various types of endocrine disturbance. Liebesny reported the maximum rise in heat production as occurring at one and a half hours after the meal in most cases, and the percentage of increase as between 22.6 and 35.3 for normal persons. His conclusions for cases of obesity are found in Table 2.

TABLE 2—*Liebesny's Conclusions for Cases of Obesity*

Class	Percentage Increase in Specific Dynamic Action *
Normal basal with normal specific dynamic action	24.9 to 36.3
Diminished basal with normal specific dynamic action	12.4 to 65.8
Approximately normal basal with diminished dynamic action	—1.2 to 15.2
Low basal with low specific dynamic action	1.7 to 11.7
Miscellaneous	6 cases varying widely

\* These figures, taken from his tables, do not agree exactly with those in the body of his paper, also shown in the foregoing.

The reports of Plaut and Liebesny appeared after our initial report on the specific dynamic action of carbohydrates had been published and while our work on protein meals was in progress. On theoretical grounds we had hoped to find just such differences in the use of food by the obese as were reported by Plaut and Liebesny.

#### METHODS

A test meal was given in the morning immediately after the determination of the basal metabolism. The carbohydrate meal consisted of from 80 to 106 gm of sucrose in the form of lemonade or of fondant flavored with mint. All patients except one had 100 gm or slightly more of sucrose. Tests were taken following this meal at intervals of thirty minutes for one hour and sixty minutes for the two following hours. The fat meal was taken in the form of slightly sweetened ice cream made from 40 per cent cream, the amount of fat varying from 55 to 129 gm. Tests were made at two-hour intervals for eight hours. The protein meal consisted of scraped beef, one or two glasses of milk, two slices of bread, and a small piece of butter, and contained from 32 to 66 gm of protein. Tests were made at two-hour intervals and continued for eight hours. The amount of fat eaten by each subject was determined separately, but for carbohydrate and protein the figures were calculated from the tables given by Rose.<sup>13</sup>

Twenty-six tests were made on twelve obese subjects, using the Tissot gasometer apparatus. Of these twenty-six tests, eleven were made with the protein meal, eleven with the carbohydrate meal and four with the fat meal. These people varied in weight from 37 per cent to

13 Rose, M. S. *A Laboratory Handbook for Dietetics*, Revised Edition, 1922.

TABLE 3—Effect of Ingestion of Protein on Heat Production

Subject	Sex	Age, Years	Height, Cm	Kg	Calories per Square Meter per Hour											
					Weight		Basal		2 Hours After Meal		4 Hours After Meal		6 Hours After Meal		8 Hours After Meal	
					Per Cent Difference from Normal	Protein Intake, Gm	Calo-ries	Per Cent Difference from Basal	Calo-ries	Per Cent Difference from Basal	Calo-ries	Per Cent Difference from Basal	Calo-ries	Per Cent Difference from Basal	Calo-ries	Per Cent Difference from Basal
R K	♀	26	148.5	76.4	+45.1	42.6	42	+14.3	47	+10.0	43	+2.1	43	+1.4	45	+5.1
M N	♀	29	155	93.6	+72	36.8	30	-18.9	21	-20.1	23	-23.7	23	-24.8	32	+5.6
F F	♀	34	163.8	101.2	+61	65.3	39	+6.3	37	-5.6	39	+0.8	38	-1.6	42	+7.0
S A	♀	25	149.5	82.3	+56	44.8	37	-0.2	43	+15.1	39	+5.4	38	+1.8	36	-3.0
A D	♀	16	169.5	84.6	+37	60.4	41	-4.0	41	+6.5	40	+12.0	43	+4.3	43	+5.3
E M	♀	12½	160.5	97.8	+95	41.6	41	-11.6	42	+1.9	42	+1.6	39	-1.7	40	-3.5
I R	♀	12½	161.5	98.6	+91	44.5	36	-3.0	44	+9.8	43	+8.0	40	+0.1	40	+1.0
L M	♀	27	148.5	75.5	+43	40.8	34	-8.3	39	+0.8	42	+15.7	39	+0.1	37	+4.2
P K	♀	32	171.1	103.1	+58	39.1	34	+2.1	35	+2.1	35	+5.7	35	+3.5	33	-0.6
F S	♀	31	165	118.1	+91	53.8	48	+31.2	46	-1.3	42	-13.1	44	-7.7	44	-8.3
S S	♀	23	165	85.5	+42	32.0	35	-5.0	38	+9.0	36	+3.0				
Average		25			+63.3	46.6	38	0.1	40	+3.1	39	+1.7	38	-1.9	39	+1.3
M A	♀	25	166.2	47.3	-22	35.8	31	-16.2	39	+25.7	38	+22.9	35	+12.7	32	+3.1
M A	♀	25	166.2	47.3	-22	64.9	33	-11.9	36	+11.2	38	+17.3	38	+15.8	35	+8.9
B MeC	♀	31	170	47.3	-28	43.9	36	-2.0	45	+26.1	46	+27.3	40	+11.6	41	+14.7
T B	♀	26	159.5	46.4	-23	54.5	41	+9.7	48	+19.2	47	+14.9	41	-1.7	40	-1.3
D B	♀	21	159.4	41.6	-26	78.3	38	+3.3	42	+10.2	43	+11.5	45	+17.2	44	+14.6
S S	♀	12	173.4	50.2	-31	58.2	36	-6.7	46	+28.9	46	+29.1	42	+16.0	42	+17.1
Average		23			-25.1	55.9	36	-4.0	43	+20.2	43	+20.5	42	+12.5	39	+9.4
M S	♀	21	167.2	62.3	+3	53.5	34	-7.0	41	+18.8	43	+23.5	40	+16.6	40	+11.9
M S	♀	21	167.2	61.4	+2	61.1	36	-1.7	43	+18.1	43	+18.1	36	-0.4	35	-3.2
M W	♀	24	160	55.5	+1	53.1	42	+12.1	49	+17.4	48	+14.6	43	+3.4	44	+7.1
K W	♀	22	163.5	58.6	0	63.8	36	-2.8	43	+20.1	44	+21.0	42	+15.4	40	+11.8
E T	♀	22	163.8	54.2	-7	67.1	38	+5.0	43	+11.9	40	+6.1	37	-3.8	37	-4.1
J S	♀	21	161.0	57.7	+3	68.3	37	-0.9	43	+17.3	Coughed		41	+11.7	39	+6.9
Average		22			+0.5	61.2	37	+0.8	44	+17.1	44	+16.9	40	+7.2	39	+5.1

\* In this column, ♀ indicates female, ♂ male

140 per cent above normal, and ranged in age from 12.5 to 34 years. Five otherwise normal underweight subjects, ranging in age from 21 to 42 years, and in weight from 22 to 31 per cent below normal served for six tests with the protein meal, three with the carbohydrate meal, and two with the fat meal. The five normal subjects varied in weight from +3 to -7 per cent from normal, and ranged in age from 21 to 24 years. Here there were six tests with the protein meal, three with the carbohydrate meal, and three with the fat meal.

### COMMENT

The basal metabolism was discussed in a previous paper<sup>3</sup>. For convenience in handling the material this paper will be divided into three sections: (1) protein meal, (2) carbohydrate meal, and (3) fat meal.

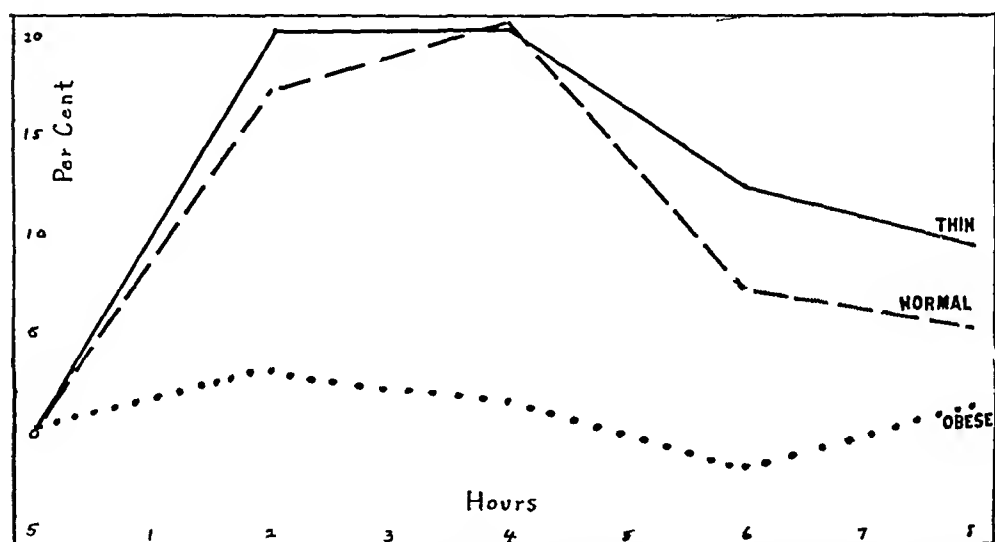


Chart 1—Average percentage increase of energy production after the ingestion of food (high protein meal)

### 1. PROTEIN MEAL

Table 3 shows that the specific dynamic action of protein in obese people is very slight. In two cases there was no increase whatever above the basal, but a decreased heat production after the protein meal. In five of the remaining nine cases the highest value occurred two hours after the meal was taken, and in the rest four hours after ingestion. The highest figure shown at any time was 15.7 per cent above the basal, and occurred after four hours. In only three of the forty-two readings were there values more than 10 per cent higher than the basal. We had no cases with normal specific dynamic action as reported by Liebesny<sup>12</sup>. At the end of six hours all values were on the decline, and at the end of the eight hour period most of them had come very near

TABLE 4—*Effect of Ingestion of Carbohydrate on Heat Production*

Subject	Sex*	Age, Years	Height, Cm	Kg	Calories per Square Meter per Hour											
					Carbohy- drate Intake, Gm	Basal		½ Hour After Meal		1 Hour After Meal		2 Hours After Meal		3 Hours After Meal		
						Calo- ries	Per Cent Difference from Basal	Calo- ries	Per Cent Difference from Basal	Calo- ries	Per Cent Difference from Basal	Calo- ries	Per Cent Difference from Basal	Calo- ries	Per Cent Difference from Basal	
R K	♀	26	148.5	78.3	106.2	17	+26.7	15	-3.5	51	+9.3	41	-5.7	42	-10.0	
S S A	♀	25	149.5	80	106.1	41	+11.3	15	+8.7	43	+3.0	42	+0.9	42	+0.7	
F P	♀	34	163.8	101.2	103.1	31	-7.6	13	+26.1	40	+17.1	38	+11.2	37	+10.3	
A D	♀	16	169.5	82.4	104.3	38	-13.1	12	+10.0	41	+6.6	44	+15.9	39	+1.5	
M S	♀	33	159.5	140	103.4	38	+4.3	17	+22.3	43	+12.0	44	+14.4	42	+9.0	
E M	♀	12½	161.5	100.9	104.5	11	-11.9	50	+23.0	49	+20.3	12	+2.7	40	-3.3	
L S	♀	34	165	117.8	100	43	+18.0	17	+7.7	39	+18.2	45	+3.4	42	-3.0	
S S	♀	28	165	83.7	100	33	-10.0	13	+30.3	39	+2.7	39	+18.2	36	+9.1	
S S	♀	28	165	84.1	100	37	-3.8	39	+5.4	38	+2.7	36	-2.7	37	0.0	
S S	♀	28	165	85.5	100	39	+6.0	42	+7.7	40	+2.6	37	-5.1	36	-7.7	
S S	♀	28	165	86.4	100	37	-1.0	43	+16.2	38	+2.7	38	+2.7	36	-2.7	
Average		27			100.8	30	+1.1	44	+11.0	42	+8.8	41	+5.1	39	+0.4	
S S	♂	38	173.4	50.9	100	37	-5.7	41	+10.8	41	+10.8	42	+13.5	41	+10.8	
K	♂	25		61.4	100	35	-11.0	39	+11.4	36	+2.0	40	+14.3	34	-2.9	
B D	♂	21	158.8	41.6	106.5	35	-5.2	41	+17.7	43	+23.6	41	+25.5	43	+22.7	
Average		28			102.2	36	-7.3	10	+13.3	40	+12.4	42	+17.8	39	+10.2	
M W	♀	21	160	55.5	101.9	39	-4.3	46	+17.9	45	+17.2	44	+14.4	41	+5.7	
D K	♀	22	163.5	58.2	104.1	33	-10.9	43	+29.6	42	+28.0	41	+23.1	36	+8.5	
J S	♀	21	161.3	58.2	106.0	37	+1.0	18	+28.2	46	+23.9	41	+9.6	37	-0.5	
Average		22			105.1	36	-4.7	46	+25.2	44	+23.0	42	+15.7	38	+4.6	

\* In this column, ♀ indicates female, ♂ male

the basal value Individual differences were counterbalanced in the general average, which showed a value of only 3.1 per cent above the basal at its highest point, two hours after the ingestion At the end of the period the average value was within 1.3 per cent of the basal

Thin people showed a very different specific dynamic action of protein from that reported above The least increase two hours after the meal was 10.2 per cent and the maximum 28.9 per cent over the basal Four of the six cases gave the highest value four hours after the meal, and the greatest increase over the basal was 29.1 per cent With the exception of one case the heat production was still above the basal at the end of eight hours The average figures for the four two-hour periods following the meal were as follows 20.2, 20.5, 12.5 and 9.4

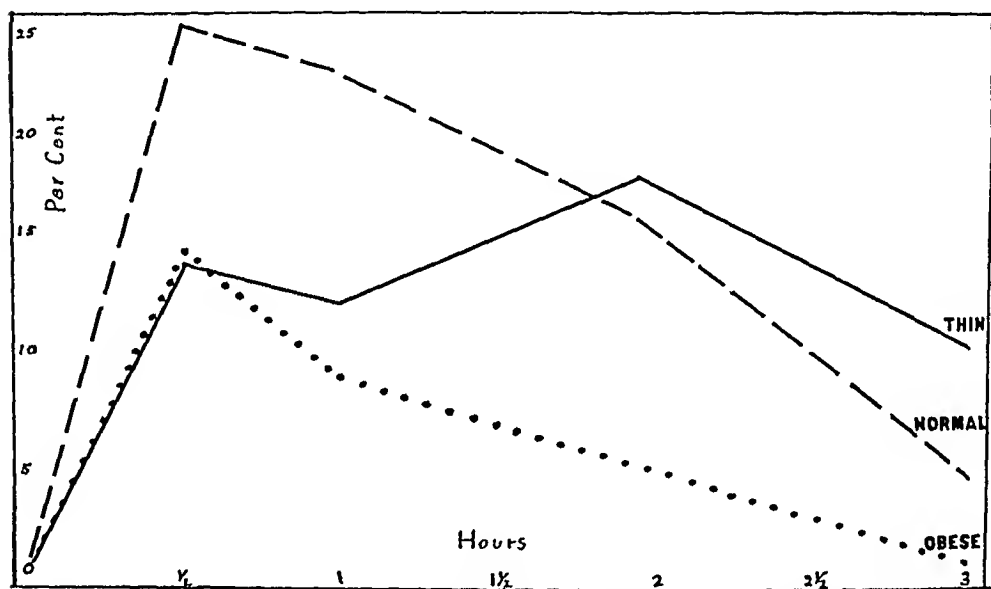


Chart 2—Average percentage increase of energy production after the ingestion of food (high carbohydrate meal)

per cent above the basal It is interesting to note that the highest specific dynamic action was shown by the subject who was most underweight

Normal people (Table 3), on the whole, showed a reaction approximately like that of thin people Two hours after the meal the increase ranged from 11.9 to 20.1 per cent above the basal, with an average of 17.1 per cent The corresponding figures for the four-hour period were from 6.1 to 23.5 per cent, with an average of 16.7 per cent above the basal After this period there was a steady decline until at the end of eight hours the average was still 5.1 per cent above the basal The changes described are shown graphically in Chart 1

There is apparently no relation between the amount of protein intake and the specific dynamic action in obese, thin or normal subjects

TABLE 5—*Effect of Ingestion of Fat on Heat Production*

Subject	Sex*	Age, Years	Height, Cm	Weight		Fat Intake, Gm	Calories per Square Meter per Hour									
				Kg	Per Cent Difference from Normal		Basal		2 Hours After Meal		4 Hours After Meal		6 Hours After Meal		8 Hours After Meal	
							Calo-ries	Per Cent Difference from Basal	Calo-ries	Per Cent Difference from Basal	Calo-ries	Per Cent Difference from Basal	Calo-ries	Per Cent Difference from Basal	Calo-ries	Per Cent Difference from Basal
M S	♀	33	159.5	131.3	+136	54.7	12	+10.4	12	-1.8	11	+3.7	42	-0.9	39	-7.9
A D	♂	16	169.5	83.7	+35	100.0	17	-15.1	11	+11.2	12	+11.2	10	+8.7	12	+15.0
A D	♂	16		87.7	+46	82.8	10	-8.1	12	+5.5	42	+7.2	42	+7.0	43	+8.0
E M	♀	12½	101.5	98.0	+91	129.1	12	-0.6	10	-3.8	11	-2.1	11	-2.7	10	-4.3
Average		20			+78	93.0	10	-1.2	11	+2.8	42	+5.8	11	+3.0	41	+3.0
B D	♀	21	159.1	41.5	-26	50.7	35	-4.2	18	+8.3	37	+1.3	41	+11.0	39	+8.0
S S	♂	42	173.1	50.2	-31	53.3	38	+8.1	13	+12.0	10	+1.7	40	+5.1	41	+6.3
Average		34			-28.5	52.0	37	+2.1	11	+10.5	39	+1.5	41	+10.0	40	+8.5
M W	♀	24	160	55	-2	70.8	39	+4.9	11	+5.7	10	+2.7	43	+9.5	41	+6.7
D K	♀	22	163.5	58.2	+2	81.5	35	-4.1	38	+0.1	37	+1.0	37	+3.3	36	+0.8
J S	♀	21	160.3	57.2	+2	55.0	38	+2.1	11	+8.5	39	+3.1	10	+6.1	36	-5.9
Average		25			+0.7	73.1	37	+1.0	40	+0.8	39	+3.6	40	+6.3	38	+0.5

\* In this column, ♀ indicates female, ♂ male



The thin subject showing the greatest specific dynamic action, that is, 29.1 per cent above the basal at the end of four hours, received only 58.2 gm of protein, whereas another subject in the same group ate 78.3 gm of protein and had a maximum value of 17.2 per cent

## 2 CARBOHYDRATE MEAL

The specific dynamic action of carbohydrate is not so marked in the three groups as that of protein (Table 4). With the exception of two cases, the greatest increase in heat production in obese people occurred one-half hour after the meal. The maximum increase was 30.3 per cent over the basal and the minimum 5.4 per cent, the average increase in this period was 14 per cent. From this time the figures decreased steadily to the end of the three-hour period, when

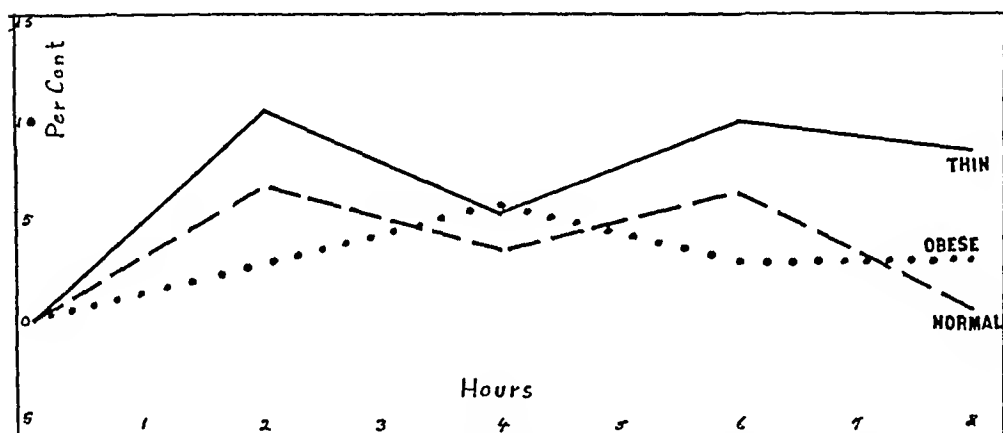


Chart 3—Average percentage increase of energy production after the ingestion of food (high fat meal)

half of the cases had returned to the basal value or lower. The average value at this time was only 0.4 per cent higher than the basal. The three thin subjects showed the highest values at the end of two hours, and two remained high after three hours. The maximum values ran from 13.5 to 25.5 per cent above the basal, with an average of 17.8 per cent. At the end of the period the highest was still 22.7 per cent above the basal, but one case had dropped to 2.9 per cent below. The normal subjects showed the greatest increase of heat production, with a curve similar in general outline to that of the obese people. The highest values, at the end of thirty minutes, ranged from 17.9 to 29.6 per cent above the basal, with an average of 25.2 per cent. At the end of the period the lowest attained were from 0.5 per cent below to 8.5 per cent above the basal, with an average of 4.6 per cent above.

The obese person does not always react to the carbohydrate meal in a characteristic manner, but the average curves show a tendency toward lessened specific dynamic action of carbohydrate (Chart 2).

## 3 FAT MEAL

With the ingestion of fat there was a slight increase in heat production in all cases (Table 5). This may have been due to the small amount of carbohydrate and protein contained in the food. The increase was slightly higher in thin people. In the obese subjects the maximum value occurred at the end of four hours, and in both normal and thin people there were two peaks, one at the end of two hours, and the other at the end of six hours. Only one normal subject showed but one peak, and that after two hours. The average maximum increase for obese people was 5.8 per cent above the basal, for thin people 10.5 per cent, and for normal subjects 6.8 per cent (Chart 3).

## SUMMARY

Twenty-six tests were made on twelve obese subjects, using protein, carbohydrate and fat meals, eleven tests on five thin people, and twelve tests on five normal subjects.

Protein showed a very slight specific dynamic action in obese people. Thin people, on the contrary, showed a very high specific dynamic action of protein. Normal subjects followed much the same course as the thin people, but to a less degree.

Normal subjects had the most marked specific dynamic action of carbohydrate. Although obese persons did not react in a uniform manner to carbohydrate intake, the average for the group indicated a lessened specific dynamic action of carbohydrate. The reaction in the three groups did not show so great a degree of difference as occurred after the protein meal.

There was very little, if any, evidence of specific dynamic action of fat.

## Book Review

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TEXTBOOK OF PHARMACOLOGY AND THERAPEUTICS, OR THE ACTION OF DRUGS IN HEALTH AND DISEASE By ARTHUR R. CUSHNY, Professor of Pharmacology and Materia Medica, University of Edinburgh Ed 8, thoroughly revised Philadelphia, Lea and Febiger Price, \$6.00

A new revised edition of this standard textbook will be appreciated by those interested in the progress of materia medica. As evidence of the progress of therapeutics, the author states that the space allotted to remedies for specific diseases is five times as great as in the 1903 edition.

The chapter on digitalis and cinchona bases has been brought up to date. A new chapter on histamin action and the relation of symptoms produced by it to anaphylaxis and a chapter on insulin and vitamins have been added.

As in previous editions, the chapter on digitalis is very complete, both in the physiologic action of the drug, its clinical use and evidence of intoxication. Vitamins are discussed in a lucid and concise manner. The presence of vitamin in cod liver oil explains its usefulness in malnutrition and rickets.

A paragraph is devoted to quinidin in auricular fibrillation and the manner of action compared with that of digitalis.

In the chapters on organotherapy, the suprarenal, pituitary, pancreas and thyroid extracts are discussed in detail. With true Scotch caution, which appeals to all those interested in the progress of therapeutics, he dismisses the remainder of organotherapy with the following sentence: "The theory on which many of these have been involved shows little advance on the belief of the savage that the courage of the lion may be acquired by eating the animal's heart, and the clinical observations which have been cited to support their use have usually been of an equally primitive order."

In spite of the additions made to certain chapters there is no increase in the size of the volume, as the descriptions of less reliable drugs have been curtailed. The author states that a textbook of this character must point out the worthlessness of certain preparations, in addition to describing the virtues of established remedies.

As a teacher he confines his discussion to relatively few important drugs, rather than confuse the student with the supposed value of a large number of practically worthless agents. This same sane method is adopted in his textbook, and this accounts in a large measure for its being accepted as a standard work, suitable for students' or practitioners' use.

## DIABETES MELLITUS

A CONTRIBUTION TO ITS EPIDEMIOLOGY BASED CHIEFLY  
ON MORTALITY STATISTICS \*

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AND  
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### INTRODUCTION

Although the term, epidemiology, has in the past been applied generally, if not exclusively, to the study of communicable diseases, so far as concerns their development among groups, or their manner of transmission from the infected or the carrier to the susceptible person, the methods of such investigations can often be employed with advantage in analyzing the causes and distribution of other diseases. The essential and distinctive feature of epidemiology is the study or knowledge of that part of the natural history of a disease which determines its occurrence or distribution quantitatively and qualitatively in groups of persons, particularly as one case of sickness is related to others, by some common factor of age, sex, race, color, occupation, geographical distribution, or determining element in heredity, environment or hygiene, distinct from the study of disease as it affects the life history of the person by modifying the structures and functions of the human body.

A limitation of accuracy in any statements based on mortality statistics must be accepted where the cause of death as given on the death certificate is without support from postmortem examination, or lacks corroboration through positive evidence of etiology as can often be obtained by direct inspection of lesions, with or without operation, or by clinical, microscopic or biologic examination of body tissues, fluids, etc, before death.

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\* From the Department of Public Health Administration of Columbia University

\* Read before the Association of American Physicians, Atlantic City, May 7, 1924, and before the Section on Preventive and Industrial Medicine and Public Health at the Seventy-Fifth Annual Session of the American Medical Association, Chicago, June, 1924

Tuberculosis is usually found to be the chief complicating fatal disease which may obscure the picture of diabetes deaths, but since tuberculosis has been, in general, steadily decreasing as a cause of death during the last fifty years, and diabetes has been increasing over the same period, we can presume that the accuracy in diabetes death rates has been increasing, so far as this factor is concerned

Where diabetes is given as a primary cause of death, the following diseases have been the chief contributing causes in the order of frequency, as shown in Table 1, for the United States Registration Area of 1917 and for the City of New York in the years 1914 and 1920

It is of some importance in this connection to recall the fact that it has been a standard practice by the Census Bureau, and by registrars of vital statistics generally throughout this country, to deal with certificates presenting more than one cause of death according to the

TABLE 1—Contributory Causes of Death in Diabetes

	U S Regis- tration Area, 1917 *	City of New York	
		1914 †	1920 ‡
Total deaths from diabetes	12,734	979	1,075
All contributing causes	6,080	316	457
Principal contributing causes	(4,480)	(297)	(282)
Gangrene	1,285		
Bright's disease	951	126	75
Organic heart disease	812	67	84
Cerebral hemorrhage	397		
Lobar pneumonia	273	15	10
Diseases of the arteries	223	26	40
Furuncle	200		
Bronchopneumonia	170	23	19
Pulmonary congestion	116		
Acute nephritis	103	9	7
Apoplexy (embolism and thrombosis)		19	25
Surgical operations		7	14
Diarrhea		5	8

\* U S Census Bureau Mortality Statistics, 1917

† Annual Report of the Dept of Health of the City of New York, 1914, p 103

‡ Annual Report of the Dept of Health of the City of New York, 1920, p 282

Index of Joint Causes of Death, U S Bureau of the Census, 1914  
According to this practice, diabetes takes precedence over all other causes with which it is reported jointly as a contributing cause, except diphtheria, pulmonary tuberculosis and typhoid fever. The error, if error there be in the inclusion of diabetes among the deaths reported from all forms of tuberculosis as a contributing cause, must indeed be small, since of 110,144 deaths from tuberculosis in the Registration Area as reported in the 1918 Census Mortality Report, pages 49 et seq, diabetes appears as a recorded complication in only 365 instances

There is no wholly reliable way of proving that deaths from diabetes are more or less accurately recognized now than they have been at any time during the last sixty years. It may, however, be accepted as probable that diabetes has shared with other causes of death in the greater accuracy of clinical diagnosis, which is chiefly responsible in

the United States for a diminution in deaths reported under those categories or titles of the International List which are unsatisfactory, because of their indefiniteness and the inclusion of many unrelated and ill-defined groups, while there has been a corresponding increase in the proportion of all deaths accurately recorded under their proper and reasonably precise titles

The frequency with which glycosuria is discovered by routine and special examinations of urine in the course of private and institutional medical practice has doubtless increased greatly in the last twenty years, and this, together with the increased frequency of blood sugar determinations, has probably caused a higher proportion of persons to be brought under medical supervision for disturbance of the function of sugar tolerance in recent years than was the case a generation ago

We should expect that the advances in early detection of mild cases of glycosuria, of high blood sugar content, and of subjectively symptomless diabetes, together with the widespread interest in dietetic adjustment and medical regulation of food habits of such persons, would have the effect of diminishing the ratio of deaths attributable to diabetes rather than of increasing them in the population

The duration of the disease, its characteristic symptomatology and the frequency with which its advanced stages bring the patient under medical care, all combine to reduce to a minimum those diagnostic errors which would lead to failure of its recognition as the cause of death

The only substantial fact that may be accepted as lending force to an argument that deaths from diabetes have in the main been recorded with as much or greater accuracy than has been the case in other important causes of death, is the experience of Cabot<sup>1</sup> with the necropsies at the Massachusetts General Hospital, who observed that among the 3,000 necropsy cases studied, there was little evidence of omission of cause, or commission of error in those stated to be due to diabetes mellitus (Other causes of death in which as high a percentage of accuracy occurred, i e, 95 per cent, were leukemia, pernicious anemia, diphtheria, puerperal eclampsia, malaria, dementia paralytica and amebic dysentery )

While the use of insulin may be postponing markedly the deaths of diabetic patients, it has not yet been shown that any permanent improvement in the death rate from this disease can be attributed solely to its use, and even if this favorable result should develop, the influence on death rates among the general population of cities or states in this country can hardly be expected to appear until at least the year 1924

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1 Cabot, Richard C Diagnostic Pitfalls Identified During a Study of Three thousand Necropsies, J A M A 59 2295 (Dec 28) 1912

Evidence has been offered by the Metropolitan Life Insurance Company<sup>2</sup> to the effect that a reduction in the death rate from diabetes among their industrial policy holders, during the last half of 1923 and the first quarter of 1924, is possibly due to the widespread use of insulin in the last year. In any event, the discovery of insulin can hardly be considered to have introduced any error into the mortality data offered in this paper.

If any particular community differs in the percentages of its population living at the various age groups from the distribution of the population by these age groups in the country as a whole, or in other cities with which death rates are compared, an adjustment of death rates for age is necessary for accuracy. In the case of New York City, whatever change there has been in the years since 1866 in the age grouping can hardly have caused any error of overestimation in the diabetes death rates, for, as a matter of fact, the City of New York in 1920 had a larger percentage of its population under 40 years of age than any city in the United States with a population of 100,000 or over. There is a considerable error in the unadjusted general death rate of the city in the direction of an understatement. Because of the relative youth of its population, the error is likewise one of underestimation to an even greater degree in the specific death rate of diabetes, from the fact, as will be seen from the study of diabetes death rates for various ages, that the rates are much higher in the later decades of life, age groups which are represented in New York City by less than the standard percentage of the population in other cities or in the Registration Area.

If there is any error in drawing conclusions from the changes in the death rates of diabetes in the last sixty years, it is likely to be due to an understatement rather than an exaggeration in the reported deaths from this cause. It is probable that this error was greater in 1866, the first year for which rates are quoted for the city of New York than in 1923.

It cannot be assumed that increase of deaths necessarily indicates an increase in the incidence of a disease, nor that an increase in the number of cases of a disease diagnosed will necessarily be expressed in an increase of the death rate of a disease, but rather the contrary, owing to the greater probability of successful arresting or curative treatment, as in the case of tuberculosis following earlier and more accurate diagnosis. In other words, the case mortality percentage of a disease which is amenable to curative resources is likely to fall as diagnosis becomes commoner in its early stages. This we may assume to have

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<sup>2</sup> Statistical Bulletin, New York Metropolitan Life Insurance Co., February, 1924.

been the case with diabetes, in which such remarkable advances have been made in diagnosis and treatment, during the last twenty years in particular

The assumption, however, is valid that an increase in the death rate of a disease may be considered as indicating an actual increase in its incidence, during a period of time when clinical diagnosis and treatment have developed progressively in the direction of greater success in recognizing and arresting it in its mild or early stages, and in postponing death in patients whose condition has progressed beyond the possibility of cure

Among the factors which have been commonly considered by students of diabetes to play any important rôle in its etiology, two, namely, obesity, or disproportionate weight for the age, sex, race and height of the person, and "nervous strain," presumed to exist when life is complicated, full of responsibility and difficult because of keen economic or industrial competition, are not revealed by the death certificate except to the extent that occupation or place of residence reported may imply a life of particular nervous hazard on the part of the deceased. Many questions of etiology receive but little illumination from mortality data unless supported by carefully prepared case histories. Similarly, the hereditary, familial or conjugal factors, if of any force in the causation of diabetes, cannot be satisfactorily studied by the use of general mortality statistics alone, and even when reliable data in a selected experience are offered in support of the theory that inheritance, family or conjugal relationships were of significance in causing diabetes such claims are commonly worthless by reason of the lack of evidence as to the dietary, occupational and other factors in the cases, which are often of more significance than the accidental relationships of birth or marriage.

Mortality data will be presented which it is believed will make clear that a consistent and great actual increase in the diabetes death rate has occurred in New York City between 1866 and 1923, and similarly in many other population groups in recent years. Some of the causative factors will be presented and discussed.

#### THE INCREASE IN DEATH RATES FROM DIABETES IN RECENT YEARS

A sufficient reason for studying the deaths from diabetes in New York City at this time is the considerable shift in relative importance, numerically, of the leading causes of death which has dropped tuberculosis from first to fourth place and has brought diabetes up to tenth place (Table 2).

Expressed otherwise, we find that while one death from diabetes was recorded in 1866 for each 2,437 deaths from all causes, in the year 1923, one death from diabetes was recorded for each fifty-one deaths from all causes.



In many of the cities of this country, where notable reduction in deaths from tuberculosis has occurred, we find there is now one death from diabetes for every four or five deaths from tuberculosis

In the registration area of the United States in the last forty years there has been a change from 28 to 16.1 in the death rate from diabetes per 100,000, of population, while the death rate from all causes has

TABLE 2—*Chief Causes of Death, City of New York, 1923*

Organic heart diseases	14,321
Pneumonia and bronchopneumonia	8,231
Cancer	6,287
Tuberculosis, all forms	5,673
Violent deaths (excluding suicide, including homicide)	4,502
Bright's disease and nephritis	4,367
Congenital debility and malformations	3,723
Diseases of arteries	3,250
Diarrhea under 5 years	1,534
Diabetes	1,360

fallen steadily during this period. There has been a still greater change in the percentage of all deaths represented by those from diabetes, in 1921 the deaths from diabetes represented 1.4 per cent of all deaths in the Registration Area, while in 1880 deaths from diabetes amounted to but 0.14 per cent of all deaths in the Registration Area of that date, a change amounting to 900 per cent of the ratio of 1880.

Of the principal causes of death in the Registration Area of the United States, 1920, diabetes appears in the twelfth place, as will be seen from the specific death rates per 100,000 given in Table 3.

TABLE 3—*Death Rates per Hundred Thousand of Population from the Chief Causes of Death in the Registration Area of the United States, 1920\**

Organic diseases of heart	141.9
Pneumonia and bronchopneumonia	137.3
Tuberculosis, all forms	114.2
Bright's disease and nephritis	89.4
External causes (violent deaths including suicide and homicide)	88.8
Cancer	83.4
Cerebral hemorrhage	80.9
Influenza	71.0
Congenital debility and malformations	69.9
Diseases of arteries	22.8
Puerperal state	19.2
Diabetes	16.1

\* U. S. Census Bureau Mortality Rates, 1910-1920.

That the importance of the increasing mortality from diabetes has long been recognized by the Census Bureau can be seen from the following quotations from the volumes on Mortality Statistics of 1906, 1907 and 1909:

1906 "Among the old Registration States there appears to be a decided tendency to an increase in mortality from this cause. These

were, in order of highest death rate, Connecticut (188), Maine (168), Massachusetts (161), New York (160), Michigan (137), New Jersey (128), Indiana (110)

"While the mortality from this disease is not great, its general increase throughout the country is significant and may be compared with the similar increase shown for cancer, a disease whose age incidence resembles that of diabetes"

1907 "This rate (139 per 100,000 for diabetes, 1907) is low as compared with the rates for tuberculosis, cancer, and other important diseases, but the mortality from diabetes is of increasing significance, as being due to a fairly well marked and distinctive type of disease and one likely to show further increase, dependent on the greater number of persons at older ages in the population. The disease is one of later middle life, is intimately dependent on the conditions affecting the nervous system, as well as the nutrition of the person, and may be one of those diseases which the sanitarians of the future will successfully restrict by directing their efforts against unhygienic conditions of living, both mental and physical"

1909 "The relative increase in the death rate from diabetes (45.5 per cent) was considerably greater than that in the death rate from cancer, but the total number of deaths from this cause was much smaller, and therefore the increase is of less importance numerically"

United States Bureau of the Census. Mortality Rates, 1910-1920, 1923, pp. 87 and 88. "For the Registration States of 1900 the death rates from diabetes show a steady trend upward, the adjusted rate for 1900 being 10.4 per 100,000 population, the rate for 1910 being 16.16, and the rate for 1920 reaching 18.7

"For both the white and colored in the Registration Area and Registration Cities, and the rural part of the Area, the death rates from diabetes increased generally in the decade (for the white, from 15.3 to 16.8 in the Registration Area, from 16.4 to 19.6 in the Registration Cities, and from 13.7 to 14.1 in the rural districts, and for the colored in the respective areas from 7 to 7.9, from 8.3 to 12.7, and from 3.2 to 5.2)"

#### DEATHS FROM DIABETES IN THE CITY OF NEW YORK FROM 1866 TO 1923

In the years from 1866 to 1923, inclusive, there were recorded by the registrar's office of the Department of Health of the City of New York, 23,254 deaths due to diabetes

Chart 1 and Table 4 give the story at a glance, and present at the same time a picture of the fall in the general death rate, i. e., the deaths from all causes for each 1,000 of the population, from 36.86 to 11.72 (a difference of 68.2 per cent), the rise in the specific death rate from

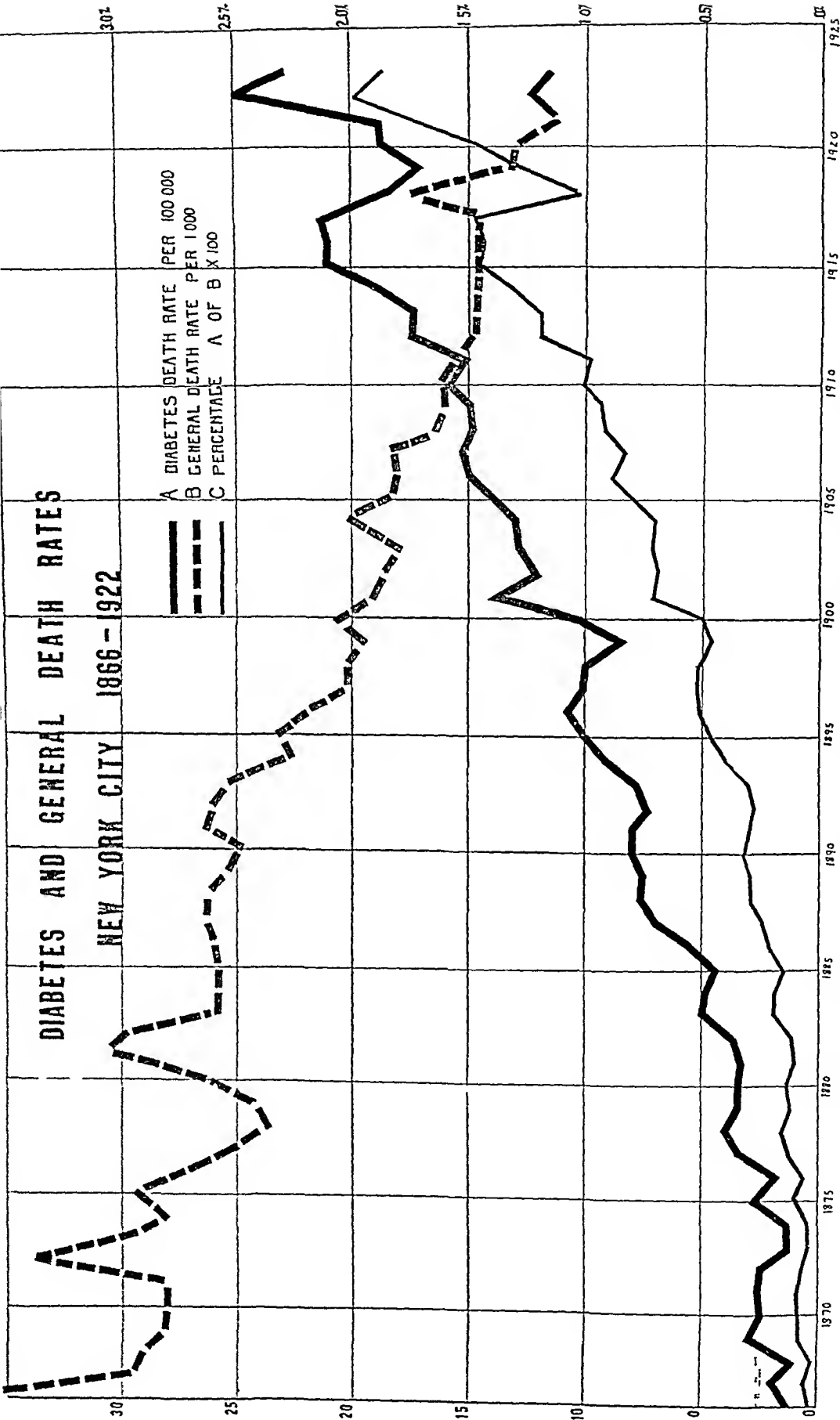


Chart 1 —Death rates from diabetes, and from all causes, New York City, 1866-1923

diabetes for each 100,000 of the population from 15 to 22.9 (a difference of 1,426.7 per cent), and the change in relation of deaths from diabetes to deaths from all causes, from 0.041 to 1.96 per cent (a difference of 4,631.9 per cent)

TABLE 4—Deaths and Death Rates, All Causes, and from Diabetes, New York City from 1866 to 1923

Year	Popula- tion	Total Deaths, All Causes	Crude Death Rate per 1,000	Diabetes Deaths			Dia- betes Death Rate per 100,000	Per centage, Deaths of All Deaths	Age Groups					
				Total	Male	Female			0 to 19		20 to 44		45+	
									M	F	M	F	M	F
1866	769,567	26,567	36.86	11	7	4	1.5	0.041	3	1	1	1	3	2
1867	812,748	23,159	31.89	14	9	5	1.9	0.061	1	1	1	4	7	0
1868	835,929	24,889	29.24	18	4	4	1.1	0.032	0	2	2	2	2	0
1869	899,100	25,167	28.08	22	13	9	3.0	0.088	2	0	6	3	5	6
1870	942,292	27,175	28.80	24	11	10	2.5	0.089	0	0	7	2	7	8
1871	962,210	26,976	28.22	25	16	9	2.6	0.093	3	2	9	2	4	5
1872	982,128	32,647	33.70	25	16	9	2.5	0.077	1	0	1	4	11	5
1873	1,002,046	29,084	29.63	13	7	6	1.3	0.015	0	0	4	1	3	5
1874	1,021,964	28,727	27.89	14	7	7	1.1	0.019	0	0	5	3	2	4
1875	1,041,886	30,709	29.40	31	21	10	2.9	0.101	1	2	9	3	11	5
1876	1,074,824	29,152	27.11	19	8	11	1.7	0.065	1	0	2	6	5	5
1877	1,117,763	26,203	23.66	35	24	11	3.3	0.134	6	1	4	4	14	6
1878	1,150,700	27,008	23.67	42	25	17	4.0	0.156	1	1	9	3	15	13
1879	1,183,638	28,342	24.13	37	21	16	3.4	0.131	2	0	4	7	15	9
1880	1,206,577	31,937	26.42	44	24	20	3.5	0.138	1	3	6	4	17	13
1881	1,246,011	38,624	30.75	43	29	14	3.4	0.111	0	0	12	1	17	13
1882	1,283,870	37,924	29.61	46	29	17	3.7	0.121	3	0	7	7	19	10
1883	1,322,880	21,011	25.81	68	34	34	5.1	0.200	2	2	12	13	20	19
1884	1,363,075	37,034	25.83	68	41	27	4.9	0.191	1	2	10	5	30	20
1885	1,404,401	35,682	25.66	63	35	28	4.5	0.177	1	1	11	6	23	21
1886	1,447,166	37,351	26.00	82	47	35	5.6	0.220	5	4	13	7	29	21
1887	1,491,137	38,933	26.33	105	52	53	7.0	0.270	1	1	7	8	44	44
1888	1,536,444	40,175	26.39	117	61	56	7.6	0.292	5*	1*	10†	8†	16	44
1889	1,566,801	39,679	25.36	118	71	47	7.5	0.297	5*	1*	13†	8†	53	38
1890	1,612,559	40,103	24.87	130	72	58	8.0	0.324	5	3	17	10	50	45
1891	1,659,654	43,679	26.31	130	64	66	8.0	0.298	2	5	10	11	72	50
1892	1,708,124	44,329	25.95	123	66	57	7.2	0.278	6	3	15	14	15	40
1893	1,758,010	44,486	25.30	137	76	61	7.7	0.308	4	3	12	19	60	17
1894	1,809,353	41,175	22.76	166	87	79	9.2	0.403	0	1	22	11	65	64
1895	1,879,195	43,420	23.18	203	95	108	10.0	0.168	3	6	21	17	71	85
1896	1,934,077	41,622	21.84	211	98	116	11.0	0.514	5	1	19	8	74	107
1897	1,990,562	38,877	20.03	202	95	107	10.1	0.520	3	5	21	13	71	89
1898†	3,438,899	66,294	20.26	345	153	192	10.0	0.521	8	7	37	26	108	159
1899	3,356,722	65,343	19.47	301	148	153	8.4	0.161	10	7	40	17	98	129
1899	3,356,722	65,343	19.47	301	148	152	8.4	0.461	10	7	40	17	98	129
1900	3,446,042	70,872	20.57	357	169	188	10.0	0.503	6	8	38	32	125	148
1901	3,544,079	70,720	19.90	503	269	234	14.0	0.712	9	2	69	37	191	195
1902	3,665,825	68,112	18.58	471	212	259	12.0	0.692	13	10	48	34	151	215
1903	3,781,423	67,864	17.95	488	232	256	12.8	0.721	2	8	57	42	173	206
1904	3,901,023	78,060	20.01	549	233	316	13.0	0.703	11	14	40	50	182	252
1905	4,025,742	73,711	18.31	589	266	323	14.0	0.799	7	11	57	47	202	265
1906	4,166,556	76,203	18.29	652	281	371	15.0	0.856	12	11	49	53	220	307
1907	4,314,237	79,205	18.36	664	291	413	15.3	0.838	13	15	35	53	203	345
1908	4,469,248	73,072	16.35	670	290	380	14.9	0.916	16	7	46	18	228	325
1909	4,632,078	74,105	16.00	696	288	408	15.0	0.939	14	15	48	52	226	341
1910	4,788,009	76,742	16.01	768	320	448	16.0	1.002	8	18	52	65	260	365
1911	4,873,211	75,423	15.48	739	316	423	15.1	0.951	14	10	59	60	213	353
1912	5,061,205	73,008	14.71	870	362	508	17.5	1.192	11	19	59	59	292	430
1913	5,049,199	73,902	14.64	884	366	518	17.5	1.196	16	18	63	52	287	448
1914	5,137,193	74,803	14.56	979	409	570	19.0	1.309	19	20	56	70	334	480
1915	5,225,189	76,193	14.58	1,109	462	647	21.2	1.455	18	21	81	69	363	557
1916	5,313,181	77,801	14.64	1,119	470	649	21.0	1.437	15	14	75	81	380	551
1917	5,401,175	78,575	14.55	1,153	473	680	21.3	1.467	15	14	74	77	384	516
1918	5,489,160	98,119	17.88	1,011	410	601	18.4	1.030	28	18	79	88	303	495
1919	5,577,163	74,433	13.35	955	389	575	17.1	1.284	18	17	71	69	291	489
1920	5,665,157	73,249	12.93	1,075	411	664	18.9	1.468	29	22	58	86	324	556
1921	5,751,859	64,257	11.17	1,120	428	692	19.0	1.74	25	25	82	74	321	593
1922	5,830,738	69,690	11.93	1,448	581	867	25.0	2.08	30	24	82	99	469	744
1923	5,927,617	69,452	11.72	1,360	512	848	22.9	1.96						

\* Age group for 1888 and 1889, from 0 to 24 years

† Age group for 1888 and 1889, from 25 to 44 years

‡ Greater City for all five boroughs 1898 and following

It will be recalled that the main factors which have brought about the reduction in the general death rate in New York have been the control of the bacterial diseases of the intestinal tract, the diminution in incidence and death rates from the acute communicable diseases of childhood, reduction in tuberculosis and infant mortality, and great improvement in the economic and sanitary standards of housing and food supplies

In the course of the increase in death rates from diabetes over this long period, there are two periods of sudden and considerable reductions in the rates, followed by even more rapid rises to higher rates than before the fall. The first of these sudden falls and rises coincided with the period of the influenza epidemic from 1898 to 1901, and in all probability represents the effect of this highly fatal infection on persons of the ages chiefly afflicted by diabetes, *i. e.*, those over 40 years of age who suffered particularly in that epidemic. Many persons who would have died of diabetes were carried off by influenza during the years in question.

The halt in the increasing diabetes death rate, which occurred in the years 1916 and 1917, was followed by a sharp drop in 1918, 1919 and 1920, the year 1922 showing the highest rate yet recorded. From experience in other countries, which suffered between 1914 and 1917 from interference and limitation in their food supplies, it seems probable that the halt in the rising diabetes death rate in 1916 and 1917 was related to the voluntary and enforced restrictions in food used, while the great drop which followed for three years was due to the influenza epidemic and the effect it had on all death rates of persons over 45 years of age, even though the heaviest mortality from influenza in this pandemic was in earlier decades of life.

In the face of the records, it is difficult to accept as a probable explanation of increasing diabetes death rates an increase of infectious or febrile diseases.

#### ANALYSIS BY AGE AND SEX

Developing this general statement of deaths to give those facts which are essential to any complete picture of a disease, we offer an analysis of deaths by age and sex.

In Charts 2, 3 and 4 and Tables 5 to 16 the facts are set forth.

Charts 2 and 3 record graphically by the semilogarithmic and arithmetic methods, respectively, the specific diabetes death rates for three age groups in the years 1866, 1875, 1880, 1895, 1900, 1910 and 1920 for which an enumeration of the city's population provided the number of persons living at each age group. The facts of population and deaths at the different ages for these seven years will be found in Table 5.

TABLE 5—Deaths and Death Rates per Hundred Thousand Population from Diabetes in Selected Age Groups at Census Years, New York City

Year	Population			Deaths from Diabetes			Diabetes Death Rates		
	0 to 19 Years	20 to 44 Years	45 Years and Over	0 to 19 Years	20 to 44 Years	45 Years and Over	0 to 19 Years	20 to 44 Years	45 Years and Over
1866	319,654	306,339	100,846	4	2	5	1.25	0.65	4.9
1875	442,584	446,812	152,490	3	12	16	0.68	2.68	10.5
1880	495,260	519,391	190,693	4	10	30	0.81	1.93	15.7
1895	690,313	874,355	284,331	9	38	156	1.31	4.36	55.0
1900	1,356,049	1,530,239	545,478	14	70	273	1.03	4.57	50.3
1910	1,825,390	2,145,583	789,108	26	117	625	1.42	5.45	79.2
1920	2,045,984	2,483,415	1,077,844	51	144	880	2.49	5.78	81.7

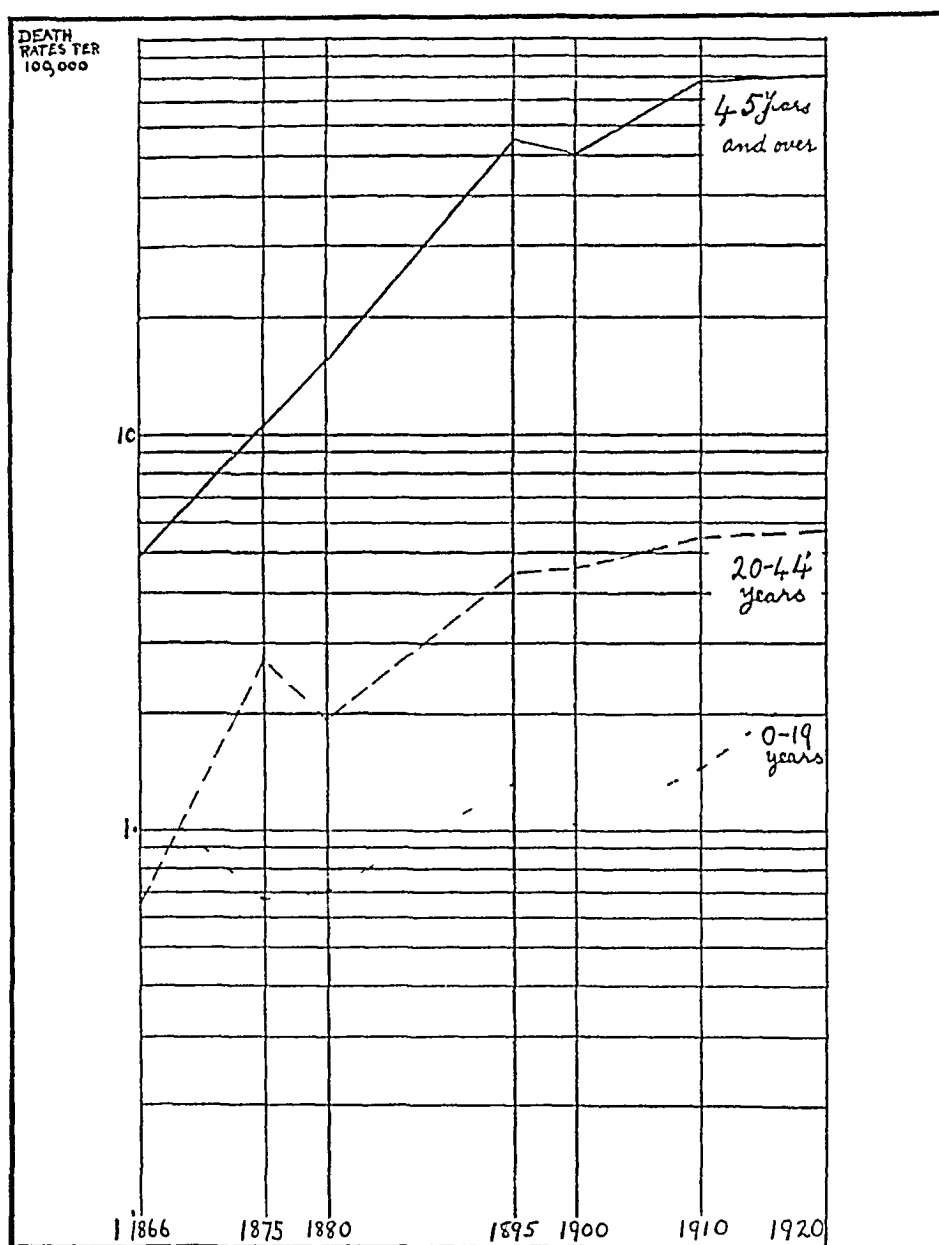


Chart 2—Death rates from diabetes per hundred thousand population, New York City, by certain age groups at census years (semilogarithmic method)

It will be seen that for each of the three age groups (from birth to 19 years, from 20 to 44 years, and 45 years and over) the net result is a marked rise in death rates, greatest among the latter decades of life and least among those of 19 years of age and under The ratio

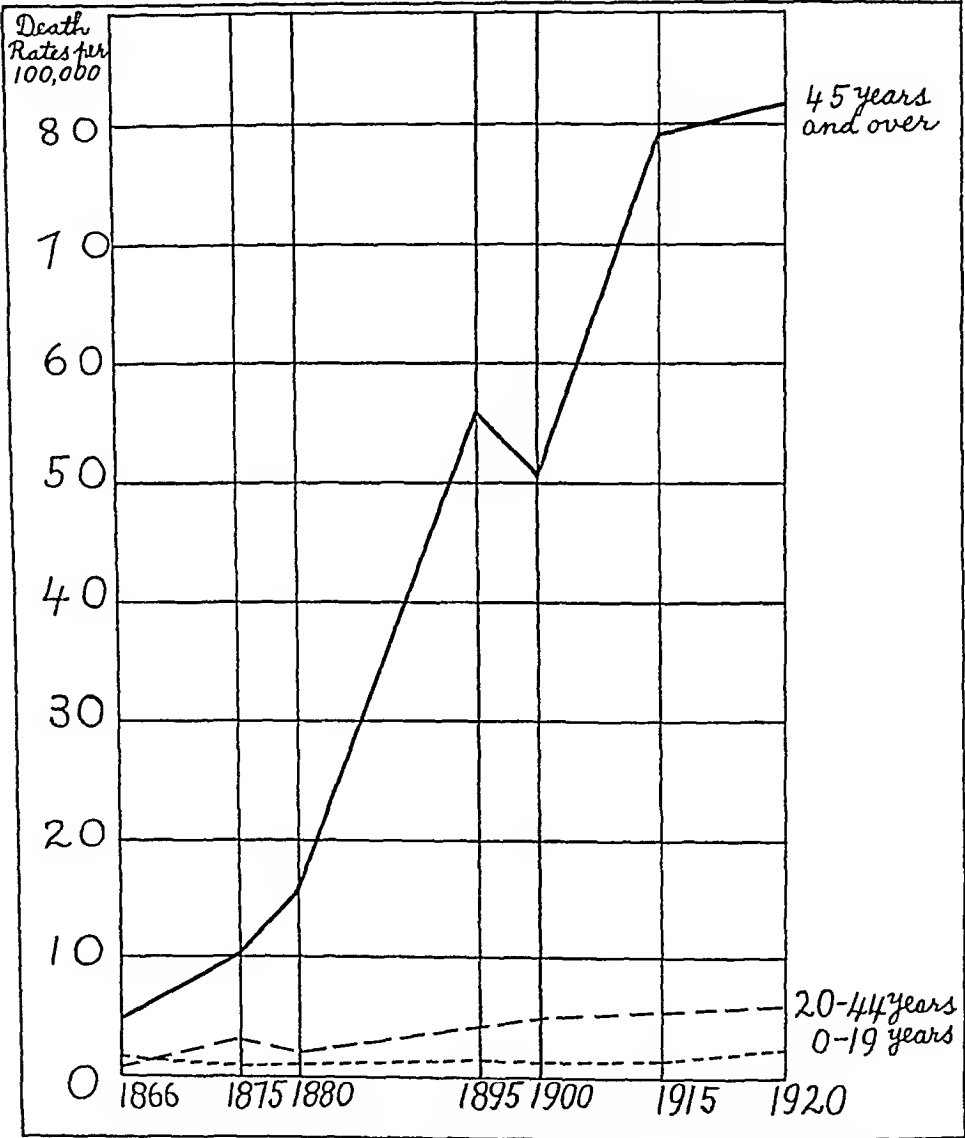


Chart 3—Death rate from diabetes per hundred thousand population, New York City

of change is expressed graphically with greater accuracy by the logarithmic Chart 2

Table 6 presents for these same seven individual census years the evidence of change in the percentages of the population and of diabetes deaths represented in the three chosen age groups, from which it will be seen that in the forty-five years (from 1875 to 1920) the percentage

TABLE 6—*Diabetes Deaths Distributed in Selected Age Groups, New York City*

Year	Percentage of All Population Represented in Each Age Group in Census Years			Percentage of All Diabetes Deaths Falling in the Same Age Groups and Years		
	0 to 19 Years	20 to 44 Years	45 Years and Over	0 to 19 Years	20 to 44 Years	45 Years and Over
1875	42.0	42.8	14.6	9.6	38.7	51.7
1880	41.0	43.0	16.0	9.1	22.7	68.2
1895	37.4	47.0	15.0	4.4	18.7	76.9
1900	39.0	45.0	16.0	3.9	19.6	76.5
1910	38.0	45.0	17.0	3.3	15.2	81.5
1920	36.0	44.0	19.0	4.7	13.4	82.0

of the population represented by the youngest age group (19 years and under) fell from 42.0 per cent in 1875 to 36.0 per cent in 1920, and that during the same time the percentage of all diabetes deaths occurring in this young group fell from 9.6 to 4.7 per cent. On the other hand,

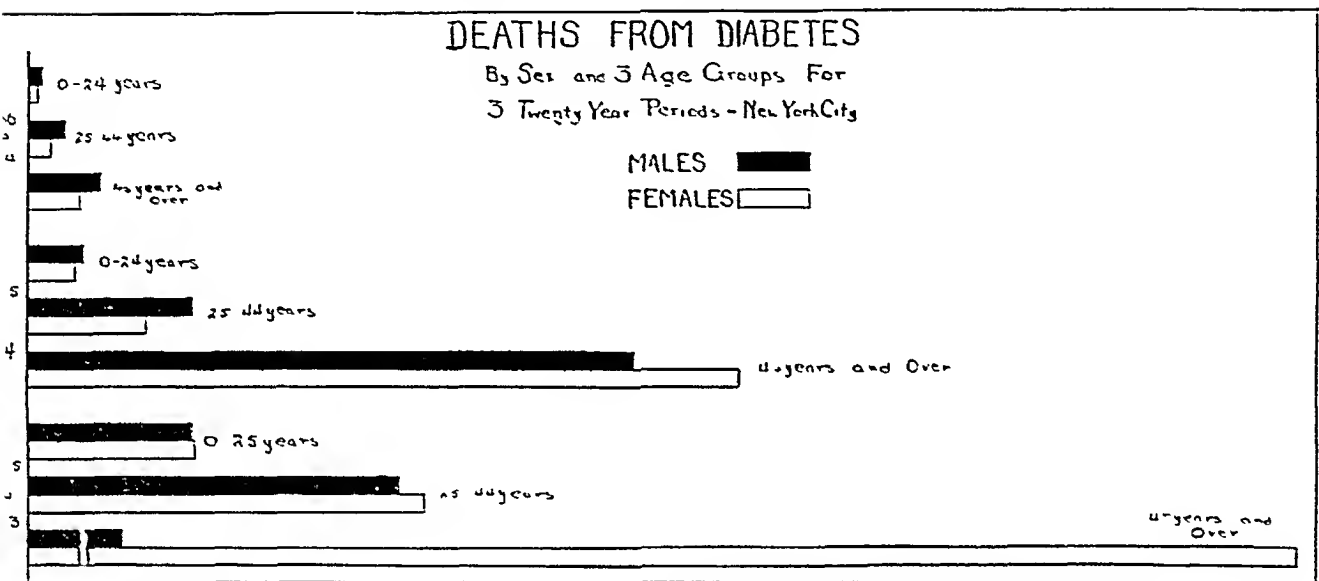


Chart 4—Deaths from diabetes by sex and three age groups for three twenty year periods, New York City

TABLE 7—*Deaths from Diabetes by Sex and Three Age Groups for Three Consecutive Periods of Years, New York City*

Year	0 to 24 Years		25 to 44 Years		45 Years and Over	
	Male	Female	Male	Female	Male	Female
1865 to 1884	39	25	103	68	206	148
1885 to 1904	160	130	464	339	1,711	2,000
1905 to 1923	468	473	1,045	1,118	5,763	8,994

the age group of 45 years and over represented 14.6 per cent of the entire population in 1875 and 19 per cent in 1920, during which time the percentage of diabetes deaths occurring at these ages rose from 51.7 to 82 per cent.

Again from a study of Chart 4 and supporting table (Table 7), it will appear that while the deaths of males from diabetes exceeded those



of females at each of the chosen age groups in the 19 years, from 1866 to 1884, in the period from 1905 to 1923, the deaths of females from this cause outnumbered the males at each age group, and to a greater degree at advancing ages, and out of proportion to changes in the sex distribution of the population. In 1920 the difference in percentages of male and female populations of New York City was only 0.2 per cent.

TABLE 8—*Percentage of Diabetes Deaths Occurring in Specific Age Groups in New York City, by Periods of Years and Individual Years by Sex, to Show What Percentage of the Diabetes Deaths Occur at Certain Ages, and in Each Sex*

Year	Sex	0 to 19 Years per Cent	20 to 44 Years per Cent	45 to 64 Years, per Cent	65 Years and Over, per Cent
1866 to 1887	Male	7.2	29.9	43.2	19.4
	Female	6.5	26.9	41.8	24.7
	Total	6.9	28.7	42.7	21.7
1890 to 1900	Male	4.62	22.4	46.0	26.9
	Female	4.4	14.5	48.4	32.7
	Total	4.5	18.3	47.1	29.9
1901 to 1917	Male	3.9	17.6	51.2	27.3
	Female	3.1	12.8	51.7	32.4
	Total	3.4	14.8	51.5	30.3
1918	Male	6.8	19.3	48.7	25.1
	Female	2.99	14.6	51.7	30.6
	Total	4.5	16.5	50.6	28.4
1919	Male	4.7	18.7	45.2	31.3
	Female	2.95	12.0	49.0	35.9
	Total	3.6	14.7	47.5	34.2
1920	Male	7.06	14.1	49.2	29.7
	Female	3.3	12.9	50.1	33.8
	Total	4.75	13.4	49.7	32.2
1921	Male	5.8	19.2	49.1	25.9
	Female	3.6	10.7	54.6	31.1
	Total	4.5	13.9	51.8	29.1
1922	Male	5.2	14.1	49.5	31.1
	Female	2.77	11.4	52.7	33.2
	Total	3.7	12.5	51.3	32.4

Table 8 confirms the story of the former tables to the effect that during the last 57 years in New York City, the proportion of all diabetes deaths under 20 years of age has remained about stationary, with the proportion of deaths among males higher in the first 20 years of life. At the ages of 45 years and over, the proportion of all diabetes deaths has increased, and those of females at a greater rate than those of males.

The great increase in specific diabetes death rates by age groups for females after 45 years of age is seen with even more detail in Table 9, although the period for comparison is only the ten years between 1910 and 1920.

It would appear that after the age of 45 among men, the situation in New York City so far as diabetes is concerned had improved, except for the age group 75 years and over.

TABLE 9—*Diabetes Death Rates per Hundred Thousand by Sex and Age Groups, 1920 and 1910, New York City*

		Both Sexes		Males		Females	
		1920	1910	1920	1910	1920	1910
All ages	Adjusted	17.0	23.9				
	Crude	23.63	18.78	18.41	15.95	28.82	21.60
Under 5		1.6	0.6*	1.8	0.8*	1.4*	0.4*
5 to 9		3.2	0.9*	4.1	0.9*	2.2	0.9*
10 to 14		3.2	1.7	2.8	0.9*	3.6	2.4
15 to 19		3.3	2.4	4.1	0.9*	2.6	3.7
20 to 24		4.2	2.8	1.6*	2.4	6.4	3.2
25 to 34		4.87	4.4	4.6	3.8	5.1	5.1
35 to 44		10.2	9.8	8.8	8.4	11.7	11.4
45 to 54		46.1	45.3	37.9	39.4	54.8	51.6
55 to 64		131.7	128.4	96.3	107.5	167.1	148.4
65 to 75		236.7	192.7	178.7	188.0	287.3	196.8
75 and over		247.3	220.3	212.1	188.0	272.5	242.9

\* Rates for deaths numbering less than five, U S Census Bureau Mortality Rates, 1910-1920, p. 526

### DEATH RATES FROM DIABETES PER 100,000 POPULATION BY SEX AND AGE GROUPS IN THE U S REGISTRATION AREA AND IN NEW YORK CITY - 1920

DEATH RATES FROM DIABETES PER 100,000 POPULATION BY SEX AND AGE GROUPS IN THE REGISTRATION STATES AND NEW YORK CITY, 1920

Age	U. S. Reg. Area				New York City			
	Male	Female	Both	Rate per 100,000	Male	Female	Both	Rate per 100,000
All ages	14.83	14.83	14.83	14.83	411	411	411	23.6
Under 5	1.6	1.6	1.6	1.6	3	3	3	0.8
5-9	3.2	3.2	3.2	3.2	1	1	1	0.9
10-14	3.2	3.2	3.2	3.2	1	1	1	0.9
15-19	3.3	3.3	3.3	3.3	1	1	1	0.9
20-24	4.2	4.2	4.2	4.2	1	1	1	1.6
25-34	4.87	4.87	4.87	4.87	1	1	1	4.6
35-44	10.2	10.2	10.2	10.2	1	1	1	8.8
45-54	46.1	46.1	46.1	46.1	1	1	1	37.9
55-64	131.7	131.7	131.7	131.7	1	1	1	96.3
65-75	236.7	236.7	236.7	236.7	1	1	1	178.7
75 and over	247.3	247.3	247.3	247.3	1	1	1	212.1

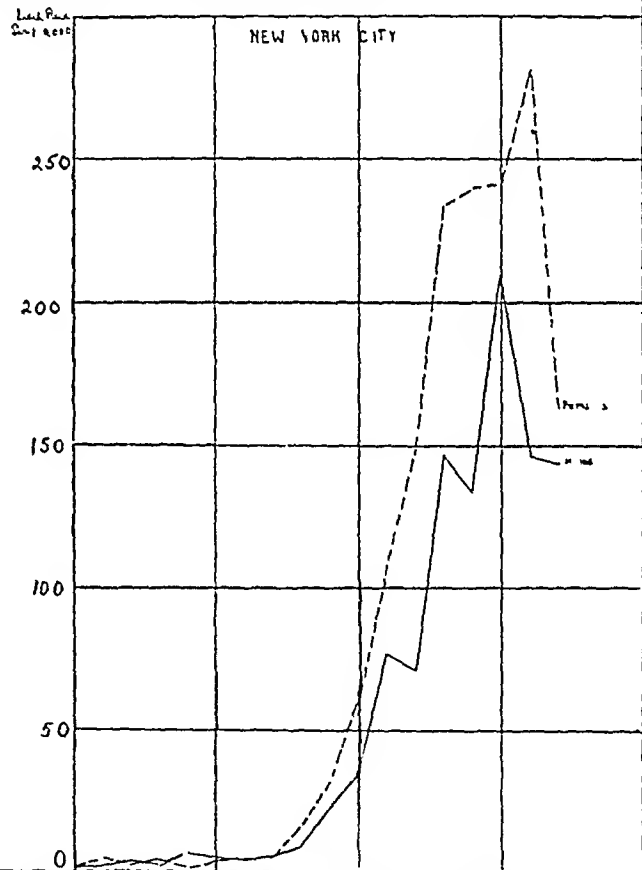


Chart 5—Deaths from diabetes by sex and five year age groups, New York City

In Table 10 and Chart 5 where the experience of the Registration States and of New York City is compared by five year age groups for 1920, it is made clear that after the age of 40 women show higher diabetes death rates, except that males in the Registration Area over 80 years of age again take the lead

TABLE 10—*Death Rates From Diabetes per Hundred Thousand Population by Sex and Age Groups in the Registration States and New York City, 1920*

Age	Registration States				New York City*			
	Deaths from Diabetes		Death Rates from Diabetes per 100,000		Deaths from Diabetes		Death Rates from Diabetes per 100,000	
	Male	Female	Male	Female	Male	Female	Male	Female
All ages	6,301	7,597	14.83	18.09	411	664	14.7	23.6
Under 5	107	79	2.32	1.75	3	3	1.06	1.08
5 to 9	126	124	2.81	2.81	12	5	4.46	1.87
10 to 14	159	196	3.81	4.76	5	9	2.01	3.65
15 to 19	203	137	5.53	3.67	9	5	4.11	2.13
20 to 24	201	176	5.57	4.62	3	18	1.20	6.08
25 to 29	209	161	5.64	4.34	10	14	3.57	4.74
30 to 34	226	202	6.62	6.19	12	11	4.57	4.39
35 to 39	252	186	7.51	6.09	14	12	5.67	5.28
40 to 44	265	273	9.68	10.7	19	31	9.71	16.88
45 to 49	392	433	15.3	19.5	38	50	22.7	32.9
50 to 54	510	695	24.2	37.1	47	82	34.6	62.7
55 to 59	662	978	41.8	68.3	69	98	76.6	110.04
60 to 64	828	1,161	63.0	97.2	48	102	70.8	147.9
65 to 69	783	1,077	87.4	127.7	56	99	146.2	233.7
70 to 74	616	854	104.5	145.0	31	66	133.5	239.5
75 to 79	459	521	129.3	138.7	25	37	209.0	240.5
80 to 84	210	242	133.9	129.5	7	16	146.1	280.0
85 to 89	71	81	122.3	108.2	85 yr and over } 3	6	143.3	162.2
90 to 94	18	15	134.6	75.6				
95 to 99	3	3	100.8	66.5				
100 and over								

\* The rates calculated on population groups as recorded in 1920 U S Census, and deaths from diabetes, as reported by New York City Department of Health

Table 11, dealing with the population of the Registration States of 1900 for the years 1900, 1910 and 1920, as well as Chart 6 for the years from 1910 to 1920, add more convincing evidence of the predominant and increasing hazard of diabetes among women and particularly among those over 45 years of age

TABLE 11—*Death Rates from Diabetes per Hundred Thousand Population in the Registration States, 1910*

Age	Both Sexes			Males			Females		
	1920	1910	1900	1920	1910	1900	1920	1910	1900
	Adjusted	Crude							
All ages	18.7	16.6	10.4	15.9	15.0	10.8	21.0	17.9	10.1
Under 5	20.6	17.6	11.0	17.3	15.8	11.3	23.9	19.5	10.7
5 to 9	2.5	2.4	2.1	2.8	2.8	2.3	2.2	2.0	1.8
10 to 14	3.3	3.5	2.4	3.6	3.3	2.2	3.1	3.7	2.5
15 to 19	4.9	4.4	4.2	4.2	4.2	4.1	5.7	4.5	4.4
20 to 24	5.3	5.3	4.5	5.8	4.9	5.6	4.7	5.7	3.5
25 to 29	5.1	4.2	4.0	5.7	4.8	3.8	4.6	3.5	4.1
30 to 34	5.6	5.6	5.0	5.9	5.8	5.3	5.4	5.3	4.8
35 to 39	9.2	9.0	6.8	9.2	9.2	7.8	9.2	8.8	5.8
40 to 44	30.0	27.2	16.4	23.8	25.5	15.5	36.6	29.0	17.3
45 to 49	80.9	75.9	40.4	63.1	63.9	37.6	99.1	88.1	43.1
50 to 54	141.5	117.8	67.2	111.0	103.2	71.1	170.6	131.8	63.5
55 to 59	153.1	118.6	68.9	149.2	103.4	88.3	156.3	122.5	51.9

\* U S Census Bureau Mortality Rates, 1910-1920, p 87

Table 12 shows how with advancing life expectancy, and possibly also in parts as a result of improved skill in medical care and earlier detection of the disease, the median age at death of diabetics has been advanced in the Registration States 21 years among men and 44 years among women in the last twenty years (from 1900 to 1920)

# DEATH RATES FROM DIABETES PER 100,000 POPULATION IN THE REGISTRATION STATES OF 1910: 1910 AND 1920

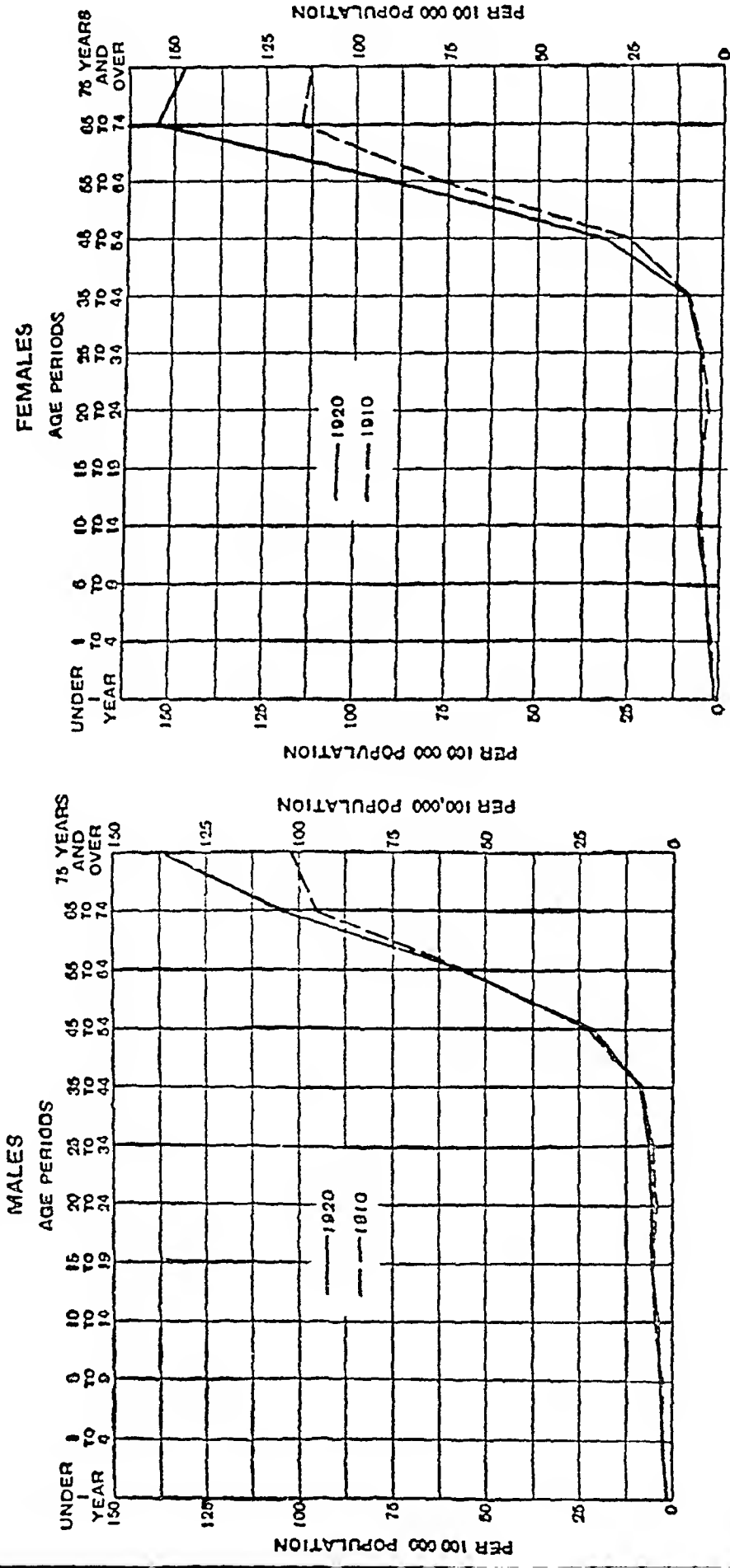


Chart 6—Death rates from diabetes, by sex, in the registration states of 1910, in 1910 and 1920

TABLE 12—*Median Age at Death from Diabetes, by Sex, in the Registration States in 1900, 1910, 1920\**

Year	Both Sexes	Male	Female
1900	57 1	57 4	56 9
1910	59 4	57 9	60 4
1920	60 6	59 5	61 3

\* U S Census Bureau Mortality Rates, 1910 1920, p 139

Averaging the five year experience of the United States for the periods from 1901 to 1905 and from 1911 to 1915 a similar picture is obtained (Table 13), although one which does not show such extreme differences between diabetes death rates of males and those of females, nor such high rates in the later decades of life as have prevailed in New York City

TABLE 13—*Death Rates from Diabetes per Hundred Thousand Population by Age Groups and Sex, Annual Averages of 1901-1905, and 1911-1915 in the Registration States of 1900\**

Age		Both Sexes		Males		Females	
		1911-1915	1901-1905	1911-1915	1901-1905	1911-1915	1901-1905
All ages	Adjusted	17 6	12 1	15 7	11 8	19 7	12 3
	Crude	19 0	12 7	16 8	12 3	21 3	13 1
Under 5		2 1	2 1	2 2	2 2	1 9	2 0
5 to 9		3 1	3 1	3 0	2 8	3 3	3 4
10 to 14		4 8	4 7	4 2	4 7	5 4	4 7
15 to 19		4 9	3 9	5 1	4 8	4 6	3 0
20 to 24		4 9	3 3	5 6	3 5	4 3	3 1
25 to 34		5 7	5 0	6 1	5 7	5 3	4 3
35 to 44		9 3	7 6	9 2	8 1	9 5	7 1
45 to 54		28 8	19 9	25 4	19 0	32 4	21 0
55 to 64		78 4	50 0	67 2	44 1	89 7	55 9
65 to 74		131 8	80 6	107 6	76 8	154 7	84 3
75 and over		133 0	80 7	123 4	84 8	140 9	77 2

\* U S Census Bureau Mortality Rates, 1910 1920, p 87

The facts before mentioned revealed by mortality statistics are particularly worth bearing in mind, when one recalls the common clinical experience that more men than women are treated for diabetes while more women than men die of this disease, in a standard population unit. This is usually explained by the fact that men more frequently submit themselves to medical examination for insurance and employment purposes, in the interest of the companies concerned or as a measure of health protection for their own sakes.

That changes in death rates from diabetes have been in process in recent years in England, and that important differences prevail between the rates for the two sexes can be readily seen by the following table, taken from the Seventy-Fifth Annual Report of the Registrar-General of England and Wales, Part III, Registration Summary Tables 1901 to 1910, p 209

TABLE 14—*England and Wales Annual Mortality from Diabetes Mellitus in Successive Decenniums, 1861-1910 per One Million Living at all Ages*

Year	Males	Females	All Persons
1861-1870	43	21	32
1871-1880	54	28	40
1881-1890	74	46	59
1891-1900	90	64	77
1901-1910	104	84	93

In distinction from the experience related in the foregoing for the United States Registration Area, the latest as well as the earliest decade reported for England and Wales shows a higher death rate from diabetes among males than among females, but it is worth noting that in a period of fifty years the death rate of females has increased in 1910 to four times their rate in 1861, while the 1910 rate for males is only 2.4 times their rate of 1861.

#### ANALYSIS BY RACE

Next to age and sex, race stock is often found to bear directly on susceptibility to a disease, or determine the fatality rate. Diabetes, often called "Judenkrankheit," because of its frequent occurrence among those of Semitic stock, appears to show at least as marked differences in persons of white and colored races and among people of the various nations who make up our population as have been found in tuberculosis.

TABLE 15—*Adjusted Death Rates from Diabetes per Hundred Thousand Population According to Country of Birth of Mother*<sup>1</sup>

Country of Birth of Mother	New York State	Pennsylvania	New York City	Chicago	Philadelphia
Ireland	23.8	17.4	26.0	24.8	18.9
Germany (and German Poland)	29.5	21.3	35.3	22.4	20.9
England, Wales and Scotland	19.5	19.2	21.4		
Italy	19.3	9.1	19.7		
United States	15.7	16.4	17.1	19.4	16.2

\* U. S. Census Bureau Mortality Rates, 1910-1920, p. 92.

In Table 15 calculations of the Census Bureau are offered, by birth of mother as a basis of race stock, from which it will be seen that in New York City the highest diabetes death rate is found among people of German or Polish stock (preponderantly Jewish). Since the stock other than white, colored or "other" (Chinese, etc.) is not entered on the death certificate, and tabulations have not been made according to religion of the deceased, it is impracticable to use even the most carefully made estimates of Jewish elements in the population of New York City or of other parts of the United States as a wholly reliable basis for calculation of death rates by race from the registrar's records. The deaths from diabetes for the year 1922 in New York City have been

tabulated according to nativity of the deceased, for foreign born whites and for native born of foreign parentage, but the percentage of Jewish persons among people coming from various countries contributing immigrants in large numbers of the United States varies too widely to permit a calculation with reasonable accuracy of the number of Jews in these two groups, to serve as a basis of racial death rates. Table 16 gives the facts as recorded.

The high death rates of 101 for Germans and seventy-five for Austrians indicate more the racial liability of the Jews from these countries living in New York than any special hazard of other races claiming these countries as their birthplace. In certain groups of

TABLE 16—*Deaths from Diabetes, New York City, Nativity of Deceased and Rates per Hundred Thousand Population of Different Nationalities (Census 1920)*

Birthplace	Nativity of Deceased	
	Deaths	Death Rate
United States	31	70
Negroes	536	15
White	106	52
Ireland	196	101
Germany	98	25
Italy	203	42
Russia	28	39
England	95	75
Austria	29	45
Hungary	11	51
Scotland	10	40
British America	12	52
France	21	55
Roumania	16	11
Poland	14	42
Sweden	2	8
Norway	4	44
Denmark	3	34
Other West Indies	2	9
Greece	31	28
Other foreign		
Total	1,448	24.8

Jewish people it is probably true in New York City that the diabetes death rate among them exceeds their tuberculosis death rate.

We can, however, show a very interesting correlation for both New York City and Boston between the increase in the percentage of Jews in the population over a period of years, and the increase in diabetes death rates for the same years in these two cities, in Table 17.

It certainly would seem to be more than an unrelated coincidence that a city of the United States, with more than half of all the Jews of the country, and at present including Jews to the extent of not less than 29.23 per cent of its population, has shown in the last thirty years a greater increase in diabetes death rates than any other large city in the country and a percentage increase of rate running closely parallel with the percentage of difference in the Jewish element in the population.

TABLE 17—*Death Rates from Diabetes in Relation to Percentage of Jews in Population*

	New York City		Boston	
	Jews in Population,* per Cent	Diabetes Death Rate per 100,000 Total Population	Jews in Population,† per Cent	Diabetes Death Rate per 100,000 Total Population†
1890	11 98	8 0		
1897			4 3	12 2
1900	17 39	10 0	4 8	13 7
1910	26 28	16 0	8 8	21 4
1913			8 9	21 3
1920	29 23	18 9		
Percentage of increase	144	136	107	74

\* American Jewish Year Book, 1923-1924, Greater New York 1920, N Y C 1920 Census Committee, p 838

† Morrison Boston M & S J 175 54, 1916

A valuable piece of evidence as to the special hazard of diabetes among the Jews is to be found in a study by Billings<sup>3</sup> of vital statistics of 60,630 persons in selected Jewish families throughout the United States, among whom he shows that of certain important diseases, diabetes had a much higher rate in Jews than among the general population. The ratios calculated from his records show deaths from diabetes to be seven times as common in Jewish males in 1889 as in males in the general population of 1880, with the corresponding ratio for females of 16 to 1.

Until we have reported by physicians cases of diabetes by age, sex, race and occupation on the occasion of establishing a diagnosis, we shall hardly be able to give much more reliable evidence than this of the exact excess liability of Jews to this disease. Any individual clinical experience, however large, can never be free from a certain accidental selection as to source of patients which cannot be trusted to run parallel with the race distribution in the population of the community. We do not know the extent to which what may be a true racial susceptibility affects the death rate from diabetes among the Jews. Sedentary occupations, unsuitable dietary habits, luxurious living, disinclination to indulge in physical exercise, a marked tendency to obesity in men and women among the Jews, particularly after 45 years of age, may well be more definite etiologic factors in the apparent excess of diabetes death rates among the Semitic people than their race.

Among the many variable factors in the study of the influence of race stock, body weight is one which lends itself to exact measurement. For this purpose we have analyzed the weights of a group of 1,429 male industrial workers, all painters, 1,170 of them Jewish, 259 non-Jewish, where age, height and body weight have been recorded accurately in the course of a careful medical examination. In Table 18 the number of



men in each year, aged from 25 to 55, for which we have the largest number of records, is given, with the sum of the pounds of weight above the normal and those below the normal in each age group, using as normal the weights of the Medico-Actuarial Mortality Investigation, 1912. It appears from this tabulation taking all age groups together, that there is an average of 18.1 pounds overweight among the Jewish painters, and 20.5 pounds overweight among non-Jewish, or viewed in

TABLE 18—*Number of Men Overweight, from Actuarial Mortality Investigation*

Age	Jews				Non Jews			
	Number Overweight	Total Pounds Overweight	Number Underweight	Total Pounds Underweight	Number Overweight	Number Pounds Overweight	Number Underweight	Total Pounds Underweight
25	11	207	3	32	4	36	2	15
26	9	120	6	64	1	23	4	58
27	20	351	10	60	4	116	1	18
28	22	364	10	100	4	69	5	47
29	28	480	27	267	5	80	2	14
30	30	513	16	180	5	68	1	18
31	20	356	11	96	5	52	1	10
32	30	485	20	154	5	95	3	24
33	24	485	15	142	5	160	4	32
34	39	711	21	213	8	142	2	26
35	35	680	17	146	5	121	2	8
36	26	479	24	238	8	190	2	23
37	34	574	23	206	3	60	2	14
38	32	680	27	220	4	44	4	40
39	25	574	21	277	6	110	4	88
40	34	663	25	232	7	197	6	149
41	20	456	10	97	2	29	1	18
42	26	366	24	318	2	40	13	213
43	19	397	14	217	3	35	6	96
44	11	118	11	156	6	114	2	31
45	15	337	9	116	4	38	4	65
46	16	285	10	117	5	90	2	17
47	11	282	5	76	3	62	4	53
48	13	153	8	126	4	101	3	38
49	11	167	11	107	1	17	4	47
50	10	191	9	87	3	91	2	60
51	5	95	3	51	2	105	2	25
52	6	91	3	36	2	76	4	25
53	2	13	4	74			1	15
54	4	61	2	13	2	50	2	38
55	2	28	5	95	1	38		
Total	590	10,702	404	4,313	119	2,449	95	1,325

Average number of pounds overweight Jews, 18.1, non Jews, 20.5

Average number of pounds underweight Jews, 10.6, non Jews, 13.9

Percentage of men overweight Jews, 58, non Jews, 54

Percentage of men underweight Jews, 40, non Jews, 43

another form, 58 per cent of the Jews are overweight and 54 per cent of the non-Jewish. That is, the overweight is not peculiar to the men of Jewish race in this group. Further study of similar records is required before definite conclusions can be reached. Occupation and economic state rather than race would seem from this to be the determining factors in overweight among men.

In a study of 3,100 men and women working in the needle trades (96.7 per cent of the males and 88.8 per cent of the females being

Jews), Schereschewsky<sup>4</sup> et al give data from which the following general statement may be made, namely, that the males in this employed group differ on the average hardly at all in weight, for age and height, from men of the same specifications as found by the Medico-Actuarial Investigation, while the women among the garment workers are, on the average, taking into account age and height, ten pounds heavier than women of similar specifications in the country at large

Davenport,<sup>5</sup> in the conclusions of his monograph on Body Build and its Inheritance, says "There are geographical differences in build, the heavy build of northern peoples may be due to a physiologic reaction or, in part, to a selective survival of the fleshier individuals or strains

"The diseases associated with very slender and slender build are tuberculosis, pneumonia, "nervousness," melancholia The disease associated with the very fleshy or fleshy build are diabetes, nephritis and dropsy, apoplexy, and arteriosclerosis and paralysis accompanying it, also numerous diseases of the alimentary tract"

At the other end of the scale of rates from those for the Jewish race, apparently are the negroes, and for these we have a reasonably accurate basis of their population, while among them, owing partly to economic reasons, and partly to lack of education, medical services are apt to be less prompt and less efficient than with other groups of our communities

The diabetes death rate among negroes is everywhere lower than among the whites of the same region, but it is noticeable that their rate is higher in the cities of the Registration Area and in New York City than in rural areas (Table 19) The difference between rates among the colored and those of the white portion of the population is less in cities than in the rural areas and less in 1920 than in 1910

In most of the states where rates are reported for white and colored, those for the whites are higher than those for the colored, the most striking contrast being for Florida, with a rate of 11.6 for the white and 3.6 for the colored<sup>6</sup>

It is not perhaps irrelevant to recall that the highest tuberculosis death rates in the cities of the United States have commonly been found among the negroes and the lowest among the Jews In diabetes the reverse seems to be the case

Concepcion,<sup>7</sup> in commenting on the mildness of diabetes among the Filipinos and Japanese where the disease is much more common among

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4 Schereschewsky The Health of Garment Workers, Bull 71 U S P H Service, 1915

5 Davenport Carnegie Institution of Washington, 1923, December, p 152, et seq

6 U S Census Bureau Mortality Rates, 1910-1920, p 89

7 Concepcion, I Incidence of Diabetes Mellitus Among Filipinos, J Philippine Island M A 2 57 (March) 1922

TABLE 19—*Death Rates from Diabetes per Hundred Thousand Population in Registration States, by Race, 1920 and 1910*

Area and Year	Death Rates from Diabetes per 100,000 Estimated Population*			Percentage of Rate for Colored Less Than That for White
	Total	White	Colored	
Registration Area				
1920†	16.1	16.8	7.9	52.9
1910	14.9	15.3	7.0	54.2
Registration States ‡				
1920	16.2	16.9	8.0	52.6
1910	15.2	15.5	7.1	54.1
Cities in Registration States ‡				
1920	19.4	19.7	13.6	30.9
1910	16.8	17.1	9.7	43.2
Rural Sections of Registration States				
1920	13.1	14.1	5.2	63.1
1910	13.5	13.7	3.2	76.6
Registration Cities in Registration States				
1920	11.4	12.8	7.0	45.3
1910	12.6	13.4	6.9	48.5
All Registration Cities ‡				
1920	19.1	19.6	12.7	35.2
1910	16.0	16.4	8.3	49.3
New York City	22.9	23.2	13.7	40.9

\* Population estimated by arithmetic method to July of each year based on Federal census of April 15, 1910, and Jan. 1, 1920.

† Exclusive of Hawaii.

‡ Includes District of Columbia.

the males of the population than among the females, suggests that the orientals, particularly the Chinese, stand nervous shock better than occidental races and further that the excessive activity of the latter peoples predisposes to their higher diabetes death rates.

However, he offers little but opinion to support any such thesis and then calls attention to the largely carbohydrate diet of the Filipinos as justifying the expectation of a high diabetes rate among them, without relating the character of the diet to its total caloric content or the estimated need of calories per capita per day under the conditions of occupation, temperature and clothing which prevail among these people.

#### OCCUPATION

Of the 493 deaths from diabetes in 1922 in New York City for which occupation was recorded, the order of frequency by occupation, as well, as the facts for these by age and sex of the deceased, is given in Table 20.

Due to the fact that the record of deaths from diabetes by occupations in New York City is not uniform with the enumeration of the population by occupations as recorded by the federal census, any calculation of the specific death rates for certain occupational groups is of doubtful reliability and very crude. Tables 20 and 21 present all the information which seems to have any value for the city of New York, so far as death rates for diabetes in various occupational groups is concerned.

The term merchant, which heads the list of occupations with the largest number of deaths, includes all variety of proprietors of merchandizing stores, a great majority of whom in New York City are Jews

The very crudity of the information in this field of mortality statistics for any community or state of the United States is sufficient

TABLE 20—Deaths from Diabetes by Occupation, Sex and Age, New York City, 1922

Occupation	Total	Sex		Age				
		Male	Female	15 to 24	25 to 34	35 to 44	45 to 64	65 and Over
Merchants	72	70	2			5	37	30
Clerical	56	46	10	8	7	5	28	8
Laborers	46	46		1	3	4	26	12
Personal service	45	30	15	1	3	5	27	9
Clothing workers	42	37	5	1	1	3	28	9
Other trades	40	35	5	4	5	1	19	11
Salesmen	30	29	1	1	1	2	16	10
Railway and boats	15	15		1		4	7	3
Carpenters	12	12			2	1	5	4
Newspaper writers	11	11		1	1	5	3	1
All building work	9	9				2	6	1
Bartenders	9	9		1		2	3	3
Bakers	9	9		1	1	1	5	1
Teachers	9	3	6			1	4	4
Printers	8	7	1			1	4	3
Shoemakers	7	7					5	2
Painters	6	6			1		5	
Clergymen	6	6					4	2
Peddlers	5	5				1	2	2
Police men	5	5				2	2	1
Chauffeurs	5	5			1	3		1
Butchers	5	5					2	3
Cigarmakers	5	2	3	1			4	
Mechanics	5	5					5	
Managers	4	3	1				3	1
Physicians	4	4					3	1
Plumbers	3	3					1	2
Bankers	3	3						3
Undertakers	2	2					1	1
Trained nurses	2		2			1		1
Lawyers	2	2					2	
Civil employees	2	1	1				1	1
Machinists	2	2				1	1	
Furriers	2	2				1	1	
Blacksmiths	1	1					1	
Electrician	1	1				1		
Fireman	1	1						
Letter carrier	1	1					1	
Civil engineer	1	1					1	
Street cleaner	1	1					1	
Totals	493	441	52	21	26	52	264	130
Total diabetes deaths recorded in 1922	1,448	581	867					

This does not include thirty five deaths under 15 nor the deaths of women where occupation was given as that of housewife or other than as specified in the list above (815), nor of 140 men whose occupation was given as other than as specified in list

reason for calling attention to the few reasonably adequate sources of information on this subject, in the literature of other countries

The most reliable information is to be found in the supplement to the seventy-fifth Annual Report of the Registrar-General of England and Wales, Part IV, Mortality of Men in Certain Occupations. This report of the registrar's office deals with 132 specified occupations for males, among whom those occupied and retired of all ages from 25 to

65 years, inclusive, were enumerated in the census and among whom deaths have been tabulated by standard causes. Among thirty-one of these occupations or occupational groups the number of deaths from diabetes in all the males of all 132 occupations are represented in the deaths in the thirty-one occupation groups chosen for reporting here.

In Chart 7 will be found arranged in order the comparative mortality figures as calculated in the Registrar's report, those of the thirty-one occupations selected because of showing fifty or more deaths from

TABLE 21—*Death Rates from Diabetes in the Chief Reported Occupations, New York City, 1922*

Occupation	Number Reported U S Census		Estimated Round Numbers		Diabetes Deaths		Death Rate from Diabetes per 100,000	
	Male	Female	Male	Female	Male	Female	Male	Female
Merchants					70	2		
Clerical	137,283	68,949	140,000	70,000	46	10	33	14
Laborers					46			
Personal service (entire class)	149,623	156,667	150,000	158,000	30	15	20	9
Laborers domestic and personal service	1,515		1,600					
Clothing workers (semi skilled operators in clothing industries)	67,865	67,817	68,000	68,000	37	5	56	7
Salesmen (in stores)	87,658		90,000		29	1	32	
Railway and boats					15			
Transportation (entire class)	218,368		220,000					
Carpenters	42,478		44,000		12		27	
Newspaper writers					11			
Editors and reporters	3,364		4,000					
All building work								
Laborers	22,959		24,000					
Semiskilled operators	1,292		1,300					
Apprentices to bldg tr	5,076		6,000					
Bartenders	5,406		5,000		9		180	
Bakers	15,510		16,000		9		56	
Teachers (school)	6,048	27,546	7,000	28,000	3	6	43	21
Printers	8,094	5,428	9,000	6,000	7	1	78	17
Shoemakers	8,062		9,000		7		78	
Painters	25,439		26,000		6		23	
Clergymen	4,037		5,000		6		120	
Peddlers					5			
Policemen	11,725		12,000		5		52	
Chauffeurs	49,185		50,000		5		10	
Butchers (in slaughter houses)	1,627		1,700		5			
Cigarmakers	7,463	6,012	8,000	7,000	2	3	25	43
Physicians	9,449		10,000		4		40	

diabetes in the three year period, as well as the mortality figure for all males of the population of England and Wales for from 25 to 65 years of age, and for all occupied and retired males of these countries to serve as a level above and below which there are striking variations in mortality figures. Those listed as farmers, etc., do not include agricultural laborers, but constitute the category of farm owners and operators who are not only better off financially but, on the average, about twenty years older than the agricultural laborers who show a maximum number at the age of 25, while the farmers are most numerous at 45.

The agricultural laborers show the lowest age grouping of all the occupations listed

The category, railway guards, etc., is exclusive of engine drivers who constitute a small and highly selected class

The category, coach, omnibus service, etc., is exclusive of motor drivers and chauffeurs

It will be noted that those occupations which in the main receive relatively low return for their labor, and in which a very considerable amount of bodily exercise is necessary, have a mortality figure at or

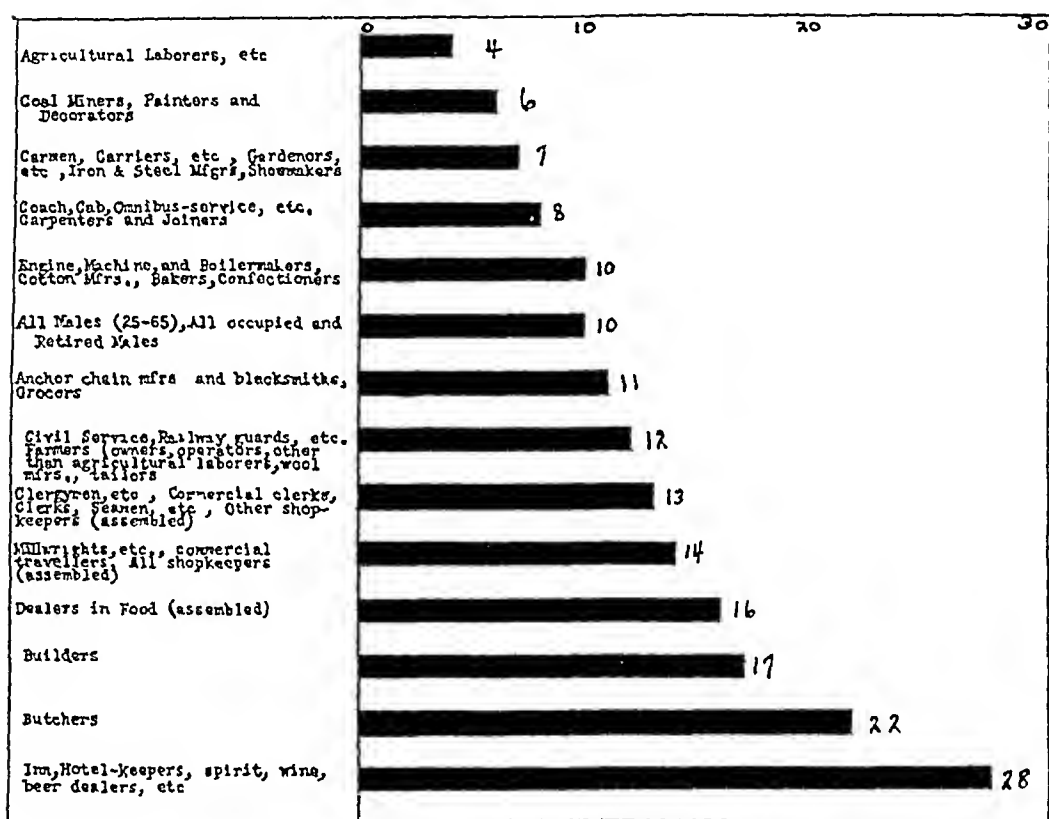


Chart 7—Comparative mortality figures for diabetes of men between the ages of 25 to 65 years, in certain occupations in England and Wales, 1910-1912, figures to right of columns death rate per hundred thousand

below the figure for all males of the same ages, whereas most of the occupations showing a higher mortality figure do not require much physical exertion and are relatively better paid

When the same basic data are presented by the Registrar in what he alludes to as social classes, which are really broad general groups by industries or occupations, not by relative incomes, the mortality figures in Table 23 are found<sup>8</sup> expressed in death rates per hundred thousand

<sup>8</sup> Supplement to the Seventy-Fifth Annual Report of the Registrar-General for England and Wales, Part IV

TABLE 22—*Comparative Mortality Figures for Diabetes, Occupied and Retired Males Aged from 25 to 65 Years, by Social Classes, England and Wales, 1910-1921*

I	Upper and middle classes	14
II	Intermediate, excluding unoccupied	14
III	Skilled workmen	9
IV	Intermediate	8
V	Unskilled workmen	8
VI	Textile workers	11
VII	Miners	6
VIII	Agricultural laborers *	4

\* Most of these are in a young age group

The best information on this subject for French experience is presented by Bertillon<sup>9</sup> in his paper on Mortality and the Causes of Death According to Occupation, from which the following is quoted

Diabetes is very common among the following occupational groups

1 In the learned professions, especially among lawyers and doctors Pharmacists and clergymen have lower, though high rates Lastly, teachers, architects and musicians have average rates

2 Occupations exposed to alcoholism, inkeepers, brewers and maltsters

3 Butchers

4 Certain other professions (dyers, commercial travelers, commercial clerks, railway clerks)

On the other hand, diabetes is very uncommon in the following occupational groups

1 Coachmen and drivers, notwithstanding they are proverbial drunkards

2 Hand laborers of all kinds, such as dock laborers, porters, general laborers, although drunkenness is very common among them

3 Railway workmen (workers on the road bed, guards, porters), but railway clerks and also engineers and firemen rise to or above the average

4 Persons engaged in agriculture (except farm tenants, who are less favored than domestic servants on the farm), gardeners and farm laborers

5 Several other manual occupations carried on in the open air (masons, shipbuilders)

6 Miners and quarrymen (except lead miners)

We find only average or insignificant figures in the metal working and textile industries, sedentary occupations, and those pursued on the water

In the main, the French experience supports the report of the Registrar-General of England, to the effect that those occupations which involve hard manual and bodily labor show low diabetes death rates

Various writers<sup>10</sup> have expressed themselves to the effect that occupations involving nervous strain and worry show high prevalence of diabetes

I am inclined to agree with Kober and Hayhurst (Industrial Health, 1924, p 972) that such an inference is doubtful, especially when lacking any control information as to race, weight, height, age and dietary

9 Transactions of the Fifteenth International Congress on Hygiene and Demography 1, Part II, pp 364-366, 1912

10 Thompson, W G Occupational Diseases, p 151 Dublin, L I Causes of Death by Occupation, U S Dept of Labor Bull 207, 1917

habits of persons supposed to be suffering a nervous strain because of their occupations. The question of first importance is, whether such persons are not overeating and underexercising, a hygienic sin, particularly common among people of sedentary, highly skilled trade or professional occupations.

Among employees of the B F Goodrich Company, rubber manufacturing establishment,<sup>11</sup> and among the steel workers in a Pennsylvania city<sup>12</sup> diabetes for the ages and sexes of the groups concerned does not exceed its incidence in the general population.

Hoogslag<sup>13</sup> says of his 250 cases (ages from 10 to 79) that occupation was an unmistakable factor, in that conditions of work favoring corpulence favored diabetes. "Captains of passenger steamers are peculiarly predisposed, as they have to preside at meals and get little exercise. Lipogenous diabetes is found almost exclusively among the well to do. Diabetes among the thin is found in the rich and poor alike, in children and especially in brain workers and in those with much responsibility."

#### MARITAL STATE

The marital state of the deceased (single, married, widowed, divorced) in those over 15 years of age, sometimes coincides with distinct differences in death rates, and in Table 23 the death rates by sex for the four usual categories are shown for the city of New York for the year 1922.

TABLE 23—*Death Rates from Diabetes per Hundred Thousand Population Over 15 Years of Age by Marital State and Sex, New York City, 1922*

Marital State	Both Sexes			Male			Female		
	Popu- lation 15 Years and Over	Deaths from Diabetes	Death Rate from Diabetes per 100,000	Popu- lation and Over	Deaths from Diabetes	Death Rate from Diabetes per 100,000	Popu- lation 15 Years and Over	Deaths from Diabetes	Death Rate from Diabetes per 100,000
Single	1,472,967	138	9.4	784,921	73	9.3	688,043	65	9.4
Married	2,328,900	805	34.6	1,178,867	379	32.2	1,150,033	426	37.1
Widowed	342,215	463	13.5	81,432	106	13.0	260,783	357	13.6
Divorced	11,420	7	61.3	4,436	4	90.1	6,984	3	42.9
Not reported	16,993			12,997			3,996		
Totals	4,172,495	1,413	33.8	2,062,656	562	27.2	2,109,839	851	40.3

Since we have not the ages of the persons whose deaths are here tabulated by marital state, speculation is idle as to the causative factors in these differences, and where the rates are astonishingly high, as among the divorced, the numbers of deaths, four for males and three

<sup>11</sup> U S P H Report No 50, 37 3083 (Dec 15) 1922

<sup>12</sup> U S P H Report No 53, 35, Dec 31, 1920

<sup>13</sup> Hoogslag, W. Nederlandsch Tijdschr v Geneesk 2 1934 (Oct 28) 1922



for females, are too small to justify any discussion. It may be that among divorced persons self-indulgence and the financial means to satisfy it are commoner than among other groups of the adult population.

#### SEASONAL VARIATION

The seasonal variation in the death rates of diabetes follows very closely the curve so generally observed in the cities and states of the northeastern United States for deaths from diseases of the respiratory

DEATH RATES PER 100,000 POPULATION FROM DIABETES  
BY MONTHS

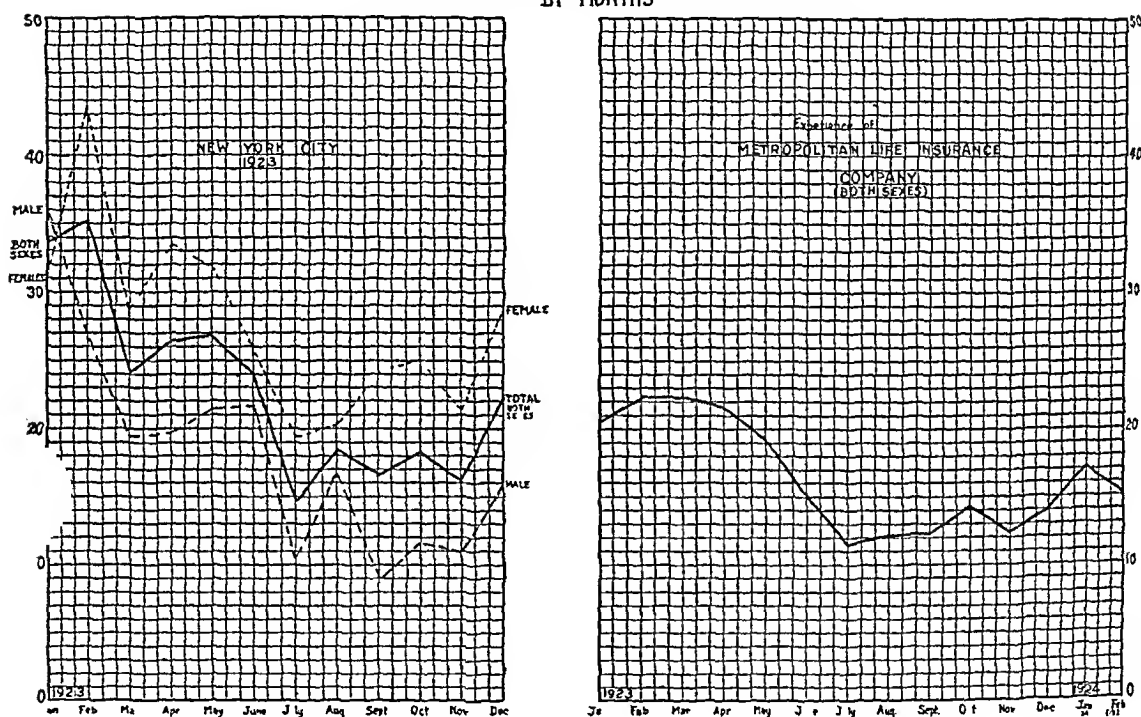


Chart 8—Seasonal variation in death rates from diabetes

tract. Diabetes shows its highest death rates from January to May and its lowest rate in July among both men and women, in the population of New York City (1923), and among the industrial policy holders of the Metropolitan Life Insurance Company (for 1923, and two months of 1924) as can be seen in Chart 8 and Table 24.

While the intercurrent affections which have a similar seasonal variation in distribution may be wholly responsible for the month of death of diabetic patients, the temperature of the months in which the climate of New York imposes the smaller demands or burden on the heat production or food intake of the body may be the reason for the low death rate, regardless of the lower incidence of respiratory tract

TABLE 24—*Deaths and Death Rates per Hundred Thousand Population from Diabetes by Months, 1923*

Months, 1923	New York City						Industrial Experience Metropolitan Life Ins Co	
	Deaths			Death Rates			Deaths	Death Rates
	Total	Male	Female	Total	Male	Female		
January	169	91	78	33.5	36.1	30.9	230	20.3
February	160	61	99	35.2	26.8	43.6	229	22.3
March	121	49	72	24.1	19.4	28.6	256	22.3
April	129	48	81	26.4	19.6	33.5	243	21.6
May	134	54	80	26.7	21.4	31.8	226	19.2
June	116	53	63	23.8	21.6	25.8	173	15.1
July	74	26	48	14.6	10.3	19.4	137	11.5
August	93	42	51	18.4	16.8	20.3	145	12.1
September	81	22	59	16.6	9.0	24.2	143	12.2
October	92	29	63	18.2	11.6	25.0	174	14.3
November	79	27	52	16.1	11.4	21.4	149	12.5
December	112	40	72	22.2	15.9	28.6	174	14.1
Total (1923)	1,360	512	848	22.9	17.1	28.3	2,279	16.1
1924								
January							213	17.2
February							178	15.2

infections so usual between June and November. That there is a distinct seasonal liability to death among diabetic patients in the winter months cannot be doubted, whatever may be the cause.

#### GEOGRAPHICAL DISTRIBUTION

If we compare the death rates from diabetes in New York City with rates for the same years in other large cities of the United States we find not only wide variation in the rates in the several cities for any one year, but remarkable differences in the percentage of increase in the rates over a period of twenty-one years as recorded in Table 25.

TABLE 25—*Death Rates from Diabetes per Hundred Thousand Population in Twenty Large Cities of the United States*

Cities	1900	1905	1910	1915	1920	1921	Average Per Cent of Rates 1900-21	Per Cent of Increase 1900-21
Baltimore	8.2	11.6	18.0	17.8	20.6	22.1	10.8	169
Boston	15.2	17.3	20.8	27.1	24.2	19.8	19.9	30
Buffalo	12.8	16.7	18.1	23.7	23.5	22.3	19.0	74
Camden	4.0	6.0	14.7	9.4	14.5	20.1	10.7	402
Chicago	6.7	11.4	15.8	17.6	20.4	20.3	14.4	203
Cleveland	4.4	7.6	13.3	16.5	17.2	17.1	12.2	288
Denver	12.7	12.3	11.7	18.2	19.7	15.6	14.3	23
Indianapolis	11.8	11.6	18.7	20.4	19.5	19.0	15.2	61
Kansas City, Mo	4.3	8.9	11.2	15.6	13.4	18.7	11.2	335
Los Angeles	11.7	11.6	14.5	19.3	16.8	23.4	15.8	100
Minneapolis	6.4	15.3	10.6	17.4	23.1	20.9	13.5	226
Newark	13.4	12.7	21.8	20.3	22.7	18.4	17.4	37
New Haven	17.6	17.3	18.6	20.8	27.4	28.1	20.6	59
New Orleans	3.5	6.4	8.5	15.6	15.7	19.8	11.1	465
New York	11.4	16.4	18.7	24.1	23.4	24.1	18.7	111
Paterson	6.7	11.7	24.6	23.6	20.5	24.0	15.7	258
Philadelphia	8.4	13.9	16.1	18.7	18.1	19.1	14.7	127
San Francisco	14.3	19.2	21.7	25.2	21.9	25.0	21.1	75
St. Louis	5.7	10.4	12.9	18.7	16.1	21.1	13.9	270
Washington	7.5	15.4	16.5	18.5	15.1	17.4	15.3	132

The cities which have had death rates from diabetes of over ten per 100,000 of population throughout the twenty-one years (from 1900 to 1921) show uniformly a lower percentage of increase in rate than do the cities which in 1920 had rates below ten, only Los Angeles and New York showing increases of 100 per cent or over among the high rate cities, the others showing percentages of increases of 127 to 465 per cent

TABLE 26—*Death Rates from Diabetes per Hundred Thousand Population by States*

Average Rates 1900 1921		Rate 1921	
New Hampshire	20.2	New Hampshire	29.0
Vermont	20.1	Maine	26.0
Nebraska	20.1	Vermont	24.7
Oregon	19.2	New York	23.4
Rhode Island	18.7	Connecticut	22.2
New York	18.4	Oregon	21.2
Connecticut	18.4	California	20.3
Maine	18.4	Massachusetts	20.2
Massachusetts	18.1	New Jersey	19.7
Illinois	17.1	Rhode Island	19.7
California	16.6	Nebraska	19.5
Kansas	16.2	Minnesota	18.1
Ohio	15.8	Illinois	18.0
Wisconsin	15.4	Ohio	18.0
New Jersey	14.8	Wisconsin	17.5
Minnesota	14.8	Pennsylvania	17.3
Michigan	14.2	Maryland	17.1
Pennsylvania	13.9	Michigan	16.5
Missouri	13.8	Indiana	16.3
Maryland	13.6	Missouri	15.9
Indiana	13.4	Kansas	15.6
Washington	13.2	Washington	15.1
Utah	12.7	Delaware	14.6
Delaware	12.2	Colorado	14.3
Montana	11.4	Utah	14.3
Colorado	11.1	Florida	10.4
Virginia	8.9	Virginia	10.1
Florida	8.8	Montana	9.9
Kentucky	8.1	Louisiana	9.4
South Dakota	7.8	Kentucky	8.7
Louisiana	7.5	North Carolina	7.5
North Carolina	7.5	South Carolina	7.3
Tennessee	6.5	Tennessee	6.1
South Carolina	6.1	Mississippi	5.8
Mississippi	5.5	South Dakota not reported	
United States	14.29	United States	16.8

There is shown a tendency to greater uniformity of rates among these large cities at the 1921 higher rates than was the case in 1900. In 1900 only nine of the twenty cities had a diabetes death rate of over ten per 100,000 population, four having rates between three and five and no city a rate as high as eighteen. In 1921 all twenty cities showed rates of at least ten and five cities had rates of over eighteen per 100,000 of population.

The variation of death rates from diabetes among the thirty-five registration states during the years 1900 to 1921 and for the year 1921, arranged in order of descending rate, is seen in Table 26 and the graphic representation of these differences in 1921 in Chart 9.

Three factors, capable of fairly exact expression which may throw light on the reasons for these variations, are the percentage of population of a state living at 45 years of age or over, in 1920,<sup>14</sup> the expectancy of life for the population of a state calculated for the end of the first

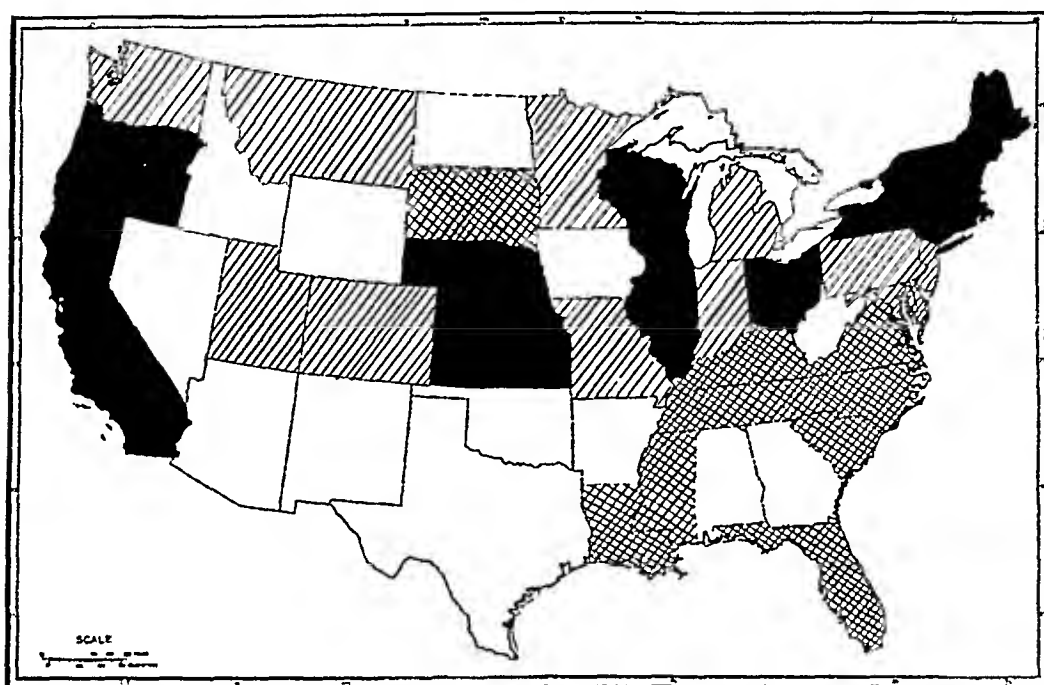


Chart 9—Average death rates from diabetes, 1900-1921, by states, solid black, average of rates, 1900-1921, over fifteen per hundred thousand, parallel lines, average of rates, 1900-1921, from ten to fifteen per hundred thousand, crossed lines, average of rates, 1900-1921, below ten per hundred thousand, and white, no record

TABLE 27—Percentage of Population Forty-Five Years and Over in United States Registration States, 1920

	Per Cent		Per Cent
Vermont	28.5	Colorado	21.9
New Hampshire	28.5	Michigan	21.7
Maine	28.1	Illinois	21.6
California	26.1	New Jersey	21.1
Indiana	24.8	Pennsylvania	20.9
Oregon	24.4	Minnesota	20.7
Massachusetts	24.2	Nebraska	20.5
Delaware	23.7	Kentucky	19.9
Rhode Island	23.3	Florida	19.4
Ohio	23.2	Tennessee	18.6
Missouri	23.1	Virginia	18.5
Washington	22.7	Montana	18.4
New York	22.5	Utah	16.6
Kansas	22.4	Mississippi	16.3
Maryland	22.3	North Carolina	16.1
Connecticut	22.2	Louisiana	16.1
Wisconsin	22.1	South Carolina	14.4

year of life, in 1920,<sup>15</sup> and the per capita income of the population of a state in 1919<sup>16</sup>

These facts are presented in Tables 27, 28 and 29

14 U. S. Bureau of Census Report, 3, 1920

15 United States Life Tables, 1921

16 Income in the United States, 1909-1919, National Bureau Economic Research

TABLE 28—Per Capita Income of States, 1919

State	Per Capita Income 1919	Death Rate from Diabetes per 100,000, 1919	State	Per Capita Income 1919	Death Rate from Diabetes per 100,000, 1919
United States	\$627		New Hampshire	\$597	16 0
District of Columbia	884	17 8	Maine	583	20 9
New York	874	21 2	Indiana	581	16 5
Nevada	850		Minnesota	581	13 6
California	820	17 3	Wisconsin	557	15 1
Delaware	792	11 3	Texas	538	
Wyoming	789		Missouri	535	13 9
Massachusetts	788	19 5	Oklahoma	534	
Washington	786	15 4	Vermont	529	24 7
Illinois	765	15 9	Utah	517	11 2
New Jersey	758	17 4	North Dakota	515	
Rhode Island	720	24 5	Montana	512	10 0
Connecticut	717	19 5	West Virginia	448	
Oregon	711	21 1	South Carolina	437	6 0
Iowa	706		Louisiana	429	6 6
Michigan	704	15 7	Virginia	429	8 4
Nebraska	702	20 7	Florida	420	7 2
Ohio	689	16 3	New Mexico	408	
Maryland	689	16 2	Georgia	394	
South Dakota	685		Kentucky	392	7 8
Pennsylvania	683	14 5	North Carolina	383	6 2
Arizona	664		Arkansas	379	
Colorado	639	10 8	Tennessee	365	6 6
Idaho	604		Mississippi	351	5 0
Kansas	602	15 2	Alabama	345	

TABLE 29—Death Rate from Diabetes by States, Related to Age and Economic Factors

State	Death Rates from Diabetes		Per Cent of Population 45 Years and Over	Per Capita Income 1919	Expectancy of Life in First Year, 1920	
	1920	Av 1900-21			Male	Female
New Hampshire	23 4	20 2	28 5	\$597		
New York	23 3	18 4	22 5	874	57 13	59 16
Maine	21 8	18 4	28 1	583		
Connecticut	21 1	18 4	22 2	717	58 45	60 33
Massachusetts	20 9	18 1	24 2	788	58 93	60 32
Nebraska	20 7	20 1	20 5	702		
Rhode Island	20 2	18 7	23 3	720		
Vermont	19 6	20 0	28 5	529		
Wisconsin	18 7	15 4	22 1	557	62 77	63 55
New Jersey	18 6	14 8	21 1	758	58 02	59 83
Illinois	17 9	17 1	21 6	765	59 19	60 81
Ohio	17 6	15 8	23 2	689	60 11	61 39
Oregon	17 5	19 2	24 4	711	60 73	62 30
Minnesota	17 3	14 8	20 7	581	61 85	62 97
California	17 1	16 6	26 1	820	57 75	61 12
Maryland	17 0	13 6	22 3	689	58 42	59 77
Kansas	16 6	16 2	22 4	602	63 14	63 48
Indiana	16 5	13 4	24 8	581	60 90	60 51
Michigan	16 3	14 2	21 7	704	59 76	59 48
Pennsylvania	16 3	13 9	20 9	683	57 93	59 68
Colorado	14 5	11 1	21 9	629		
Washington	13 9	13 2	22 7	786	60 70	62 60
Utah	13 2	12 7	16 6	517	58 77	61 18
Missouri	12 1	13 8	23 1	535	60 32	61 56
Montana	10 8	11 4	18 4	512		
Delaware	10 7	12 2	23 7	792		
Virginia	9 3	8 9	18 5	429	60 75	61 22
Florida	8 8	8 8	19 4	420		
South Dakota		7 8	18 0	685		
Louisiana	7 8	7 5	16 1	429		
North Carolina	7 7	7 5	16 1	383	61 25	60 72
Kentucky	7 5	8 1	19 9	392	60 97	60 05
Tennessee	6 2	6 5	18 6	365	61 54	60 77
South Carolina	6 2	6 1	14 4	437	59 54	60 40
Mississippi	5 8	5 5	16 3	351		
United States	16 1†	14 29†	20 8*	627	59 38†	60 63†

\* Continental United States

† Registration states

‡ Aggregate of states listed 78 per cent of total population

It will be seen that the high rates fall commonly in the states where either high age grouping of the population or high per capita income, or both are present. Where high expectancy of life is recorded for a state (1920) there is commonly a lower diabetes death rate than in states where life expectancy is shorter.

Concepcion<sup>7</sup> gives evidence of an irregular but considerable rise in diabetes mortality rates per 100,000 population in Manila, and relates this in a measure to the increase in per capita sugar consumption expressed in kilograms.

De Langen and Schut<sup>17</sup> say they find in Batavia that diabetes is particularly frequent among the idle rich.

Gajewski<sup>18</sup> reports from the Preuss. Statist. Landesamt the gradual increase in death rates from diabetes until 1914 up to 9.54, the drop during the war years to 5.9 in 1918, the fall in the rate among

TABLE 30—*Incidence of Diabetes Mellitus Among Filipinos*

Year	Death Rate from Diabetes per 100,000	Per Capita Sugar Consumption, Kilograms
1910	2.3	3.19
1911	0.9	11.09
1912	3.3	8.15
1913	0.8	17.46
1914	1.7	14.69
1915	2.1	18.18
1916	2.5	3.80
1917	3.8	17.90
1918	2.9	15.23
1919	4.2	26.19
1920	4.1	22.79

the women being greater than among the men, and the rise to 6.59 in 1921. These rates, taken together with original information copied directly from the official records in Berlin, are shown in Table 32, giving the experience for males and females in both urban and rural populations of Prussia for the years from 1906 to 1921.

Gajewski noted that where excess nutrition was prevalent before the war the diabetes death rate was highest, and that this rate fell less where food shortage during the war was slight than where there was serious privation.

The food shortage expressed itself not so much in the lack of sugar and carbohydrates as in lack of fats, which should make one suspect that it is not the quality but the gross quantity of food (calories) that plays the chief part in development of a high diabetes death rate in a community where more food is eaten than is required.

<sup>17</sup> De Langen and Schut. *Medelingen Borgelyken Genees Diente in Nederland Indie* 3:63, 1918.

<sup>18</sup> Gajewski, W. *Zur Sterblichkeit an Zuckerkrankheit in Preussen seit 1891 nebst Anhang die Eigensterblichkeit der jüdischen Bevölkerung an Zuckerkrankheit im Jahre 1920*, *Med-statist. Nachr.* 11, III and IV, 1920.

TABLE 31—*Diabetes Death Rates per Hundred Thousand Population in Prussia, by Years, Rural and Urban Distribution and Sex, 1906-1921*

Year	Urban			Rural			Whole Country		
	Male	Female	Both Sexes	Male	Female	Both Sexes	Male	Female	Both Sexes
1906	11.97	8.62	10.28	3.98	2.88	3.42	7.57	5.49	6.52
1907	12.84	8.67	10.73	4.37	3.29	3.83	8.21	5.75	7.06
1908	13.92	9.74	11.83	4.62	3.45	4.03	8.84	6.32	7.56
1909	13.84	9.64	11.67	4.51	3.38	3.95	8.73	6.24	7.44
1910	15.06	10.49	12.74	4.59	3.41	4.01	9.33	6.33	7.98
1911	14.43	10.52	12.42	5.14	3.85	4.49	9.48	7.03	8.23
1912	14.41	10.71	12.51	5.25	4.37	4.82	9.58	7.44	8.48
1913	15.18	10.91	12.75	5.76	4.67	5.21	10.23	7.69	8.96
1914	16.39	11.91	13.86	5.97	4.97	5.22	10.97	8.09	9.54
1915			(13.0)*						
1916			(14.1)*						
1917			12.1 *			4.9 *	9.6 *	7.2 *	8.4 *
1918	11.68	7.88	11.3 *			4.5 *	8.8 *	6.7 *	7.8 *
1919			9.72	5.23	3.98	4.41	8.32	5.68	6.97
1920			8.1 *			3.9 *	7.3 *	4.7 *	5.9 *
1921	9.93	6.57	8.14	4.77	3.27	3.99	7.23	4.88	6.02
	9.87	6.73	8.23	4.63	3.56	4.08	7.21	5.17	6.14
	10.27	8.04	9.16	3.93	3.57	3.75	7.22	5.99	6.59

\* Rates taken from Gajewski Zur Sterblichkeit an Zucker Krankheit in Preussen

Through the courtesy of the office of the Surgeon-General of the Army, an interesting set of facts is offered with regard to the ratio of diabetes among drafted men ("Defects Found in Drafted Men") from the various states and regions of the United States. Tables 32, 33, 34, 35, 36 and 37 dealing with drafted men are based on the examination of approximately 2,000,000 of the 2,700,000 selective service men who were entrained for camps, and 549,099 who were rejected by the local boards as physically or mentally unfit for all forms of military service. Of this number 740 were found to have diabetes, and of these 725 were rejected as physically unfit for military service.

TABLE 32—*Diabetes in Drafted Men*

State	No. of Cases	Ratio per 1,000	State	No. of Cases	Ratio per 1,000
Connecticut	44	1.23	Mississippi	10	0.27
Vermont	6	0.71	Virginia	14	0.25
Oregon	11	0.69	Washington	9	0.25
South Dakota	13	0.63	Minnesota	17	0.24
Maine	11	0.55	Missouri	20	0.23
Wisconsin	35	0.55	Ohio	33	0.23
Iowa	34	0.50	Montana	6	0.22
Arizona	4	0.48	North Dakota	4	0.22
Utah	5	0.42	Pennsylvania	45	0.22
Nebraska	12	0.41	Colorado	4	0.18
Maryland	15	0.40	Indiana	13	0.18
New York	101	0.39	Kansas	7	0.18
California	31	0.38	Idaho	2	0.16
District of Columbia	4	0.35	North Carolina	9	0.16
New Hampshire	3	0.35	Tennessee	9	0.15
Rhode Island	5	0.34	Wyoming	1	0.15
Illinois	57	0.32	Alabama	7	0.14
Massachusetts	29	0.32	Oklahoma	7	0.12
Nevada	1	0.30	Texas	12	0.10
New Jersey	22	0.29	Arkansas	4	0.09
West Virginia	11	0.28	Kentucky	6	0.09
Michigan	27	0.27	Florida	2	0.08
South Carolina	3	0.08	Delaware		
Georgia	4	0.06	New Mexico		
Louisiana	1	0.02	State not specified	10	0.11
Alaska					
Total				740	0.27

TABLE 33—*Diabetes Mellitus Distribution by Urban and Rural Communities*

	Number of Cases	Ratio per 1,000
Urban	315	0 22
Rural	425	0 20
New York City	61	0 43
Boston	6	0 30
Philadelphia	18	0 38
Chicago	31	0 38

TABLE 34—*Diabetes Mellitus*

Groups	Total Cases	Ratio per 1,000	Groups	Total Cases	Ratio per 1,000
Agricultural, native white, North, 73% plus	48	0 45	Mountain whites	12	0 16
Agricultural, foreign and native white	115	0 39	Indian, sparsely settled	5	0 16
Agricultural, native white, South	63	0 15	Mexican, sparsely settled	5	0 18
Agricultural, negro, 45% plus	23	0 13	Native white, Scotch origin	4	0 07
Eastern, manufacturing	110	0 49	Russian 10%	4	0 11
Commuters	23	0 31	Scandinavian, 10%	65	0 41
Mining	17	0 18	Finns, 10%	2	0 15
Sparsely settled, 3 or less per square mile	9	0 20	French Canadians, 10% plus	34	0 37
Desert	4	0 33	German and Scandinavian each 10% plus	49	0 50
Maritime	5	0 25	German and Austrian, 20% plus	24	0 24
Mountain	14	0 27	German and Austrian, 15% plus	125	0 36

TABLE 35—*Diabetes Mellitus, April 1, 1917, to Dec 31, 1919, Ratio per Thousand per Annum*

By Race and Rank	Admissions		Deaths		Discharges		Days Lost	
	Abs No	Rate	Abs No	Rate	Abs No	Rate	Abs No	Non-effective
Total	718	0 17	104	0 03	330	0 08	39 062	0 03
Officers	83	0 40	6	0 03	14	0 07	5 453	0 07
White enlisted	586	0 16	78	0 02	291	0 08	30 875	0 02
Colored enlisted	26	0 13	16	0 06	13	0 05	2,236	0 02
Color not stated	10		3		8		409	
Native troops	3	0 08	1	0 03	1	0 03	89	0 01
Filipino	1	0 05	0		0		47	0 01
Hawaiian	1	0 18	0		1	0 18	0	
Porto Rican	1	0 08	1	0 08	0		42	0 01
By country where serving								
United States	501	0 22	73	0 03	264	0 12	23,379	0 03
Europe	196	0 12	28	0 02	59	0 04	14,695	0 02
Other countries	21		3		7		988	

There are also presented the ratios of diabetes per 1,000 men per annum among the military personnel during the World War, and among the enlisted personnel of the Army for the decade of 1913 to 1922. The reader must be on his guard against comparing these ratios, which are based on incidence and admissions to sick call, with the death rates per 100,000 of population used very generally through the remainder of this study.

These records are of interest chiefly because of the wide geographic distribution of the basic material and the uniformity of examination, procedure and manner of life of the great mass of the men studied during the army experience. It is a matter of particular interest that the admission rates for diabetes for the ten years from 1913 to 1922



TABLE 36—*Admissions, Enlisted Men, Serving in the United States or Europe by States or Nativity, Ratio of Diabetes Mellitus per Thousand per Annum, April 1, 1917, to Dec 31, 1919*

Alaska	0		Nebraska	13	0.30
Alabama	12	0.18	Nevada	2	0.41
Arizona	0		New Hampshire	2	0.15
Arkansas	6	0.10	New Jersey	4	0.04
California	8	0.08	New Mexico	1	0.08
Colorado	4	0.12	New York	61	0.18
Connecticut	5	0.11	North Carolina	14	0.21
Delaware	3	0.42	North Dakota	2	0.08
District of Columbia	1	0.06	Ohio	32	0.17
Florida	4	0.13	Oklahoma	4	0.05
Georgia	11	0.14	Oregon	5	0.18
Idaho	1	0.06	Pennsylvania	41	0.15
Illinois	44	0.19	Rhode Island	5	0.29
Indiana	16	0.17	South Carolina	9	0.19
Iowa	16	0.17	South Dakota	4	0.14
Kansas	15	0.25	Tennessee	6	0.08
Kentucky	10	0.14	Texas	15	0.10
Louisiana	10	0.17	Utah	0	
Maine	1	0.04	Vermont	5	0.50
Maryland	6	0.13	Virginia	20	0.30
Massachusetts	14	0.12	Washington	1	0.02
Michigan	16	0.13	West Virginia	2	0.04
Minnesota	12	0.13	Wisconsin	14	0.15
Mississippi	14	0.29	Wyoming	1	0.09
Missouri	25	0.21	Others	89	
Montana	2	0.06			
Total				608	0.17

TABLE 37—*Diabetes Mellitus, U S Army, Enlisted Men, Admissions Ratios per Thousand per Annum*

	White				Colored		Native	
	U S	P I	Hawaii	Panama	U S	P I	Scouts	P R
1913	0.21	0.11		1.25				
1914	0.15							
1915	0.21							
1916	0.18	0.19		0.29	1.21			
1917	0.18	0.11		0.25	0.08			
1918	0.20	0.18	0.18	0.12	0.16		0.17	0.12
1919	0.23	0.26			0.15			
1920	0.16	0.11		0.45			0.14	
1921	0.10		0.15		0.32			
1922	0.16		0.20	0.15				0.37

show such slight variations, while the rates for every city and state of the United States have during the same period increased with great uniformity for males over 20 years of age. Obesity and physical indolence are discouraged by the hygiene and necessities of army life, whether in war or in peace.

#### DEATH RATES FROM DIABETES IN RELATION TO VARIATION IN PER CAPITA CONSUMPTION OF FOOD, PARTICULARLY SUGAR

That the general dietetic habits of people vary widely as measured in calories, and have changed in the direction of a greater liberality of food intake in recent times, must be admitted if we accept the statements of Taylor, Legendre and others on this subject. According to

Taylor,<sup>19</sup> the prewar daily per capita consumption of food in Italy was 2,560 calories, in the United Kingdom 2,860, in Germany 3,200 and in the United States 3,650 Legendre<sup>20</sup> estimates that the average per capita daily consumption of food in France has risen from 1,645 calories in 1832 to 2,255 in 1862, and to 3,160 calories in 1912

Taylor notes with regard to the United States that possibly 10 per cent of the population consumes over 4,000 calories a day without work requirements to justify this intake, and that of the industrially submerged tenth, perhaps from 5 to 10 per cent consume less than 2,000 calories a day, and he lays down the general principle that the work of prosperity increases food consumption and the idleness of hard times reduces it

It is reported by the Bureau of Animal Industry of the U. S. Department of Agriculture that the annual per capita consumption of meat has fallen in the last fifteen years from 179 to 155 pounds, this reduction having been replaced by an increase in the use of cereals, sugar, milk and fruits In contrast with this change in the United States is the reported annual consumption of 250 pounds of meat per capita in Australia

Taylor estimates that with our present food habits, which include the annual consumption of about 100 pounds of sugar per capita, we provide 500 calories a day in our average ration of 3,600 calories for all ages from sugar which we not only like particularly but find a cheap food and most effective for workers

In spite of the probability that with normal conditions of economic life no great expansion occurs in national food consumption expressed in calories as Taylor states, it is, however, probable that among certain racial, economic and age groups prosperity tends to tempt them into food habits which exaggerate the usual discrepancy between the amount of food intake and the quantity needed for their respective heat, growth, repair and work requirements

One index of the tendency of our people to use larger amounts of food is the record of per capita consumption of sugar, which is offered here not as an explanation of the increased death rates from diabetes in recent years, but more as a sign of the tendency to excesses in the use of foods of all kinds, beyond the needs of persons for foods in proportion to their expenditure of energy at the different ages of life, and in particular in the later decades

The estimated per capita consumption of sugar per annum over certain years in the United States, Great Britain and France, and the diabetes death rates for the Registration Area of the United States, for

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19 Taylor, A. E. *J. of Home Economics* **16** 55 (Feb.) 1924, *Harvard Economic Rev.* **2** 283 (April) 1924

20 Legendre *Bull. Soc. scient. d'Hyg.* **11** 161, 1923

Great Britain and for Paris (not available for France), for some of the same years is shown in Chart 10 and in Tables 38, 39 and 40 <sup>21</sup>

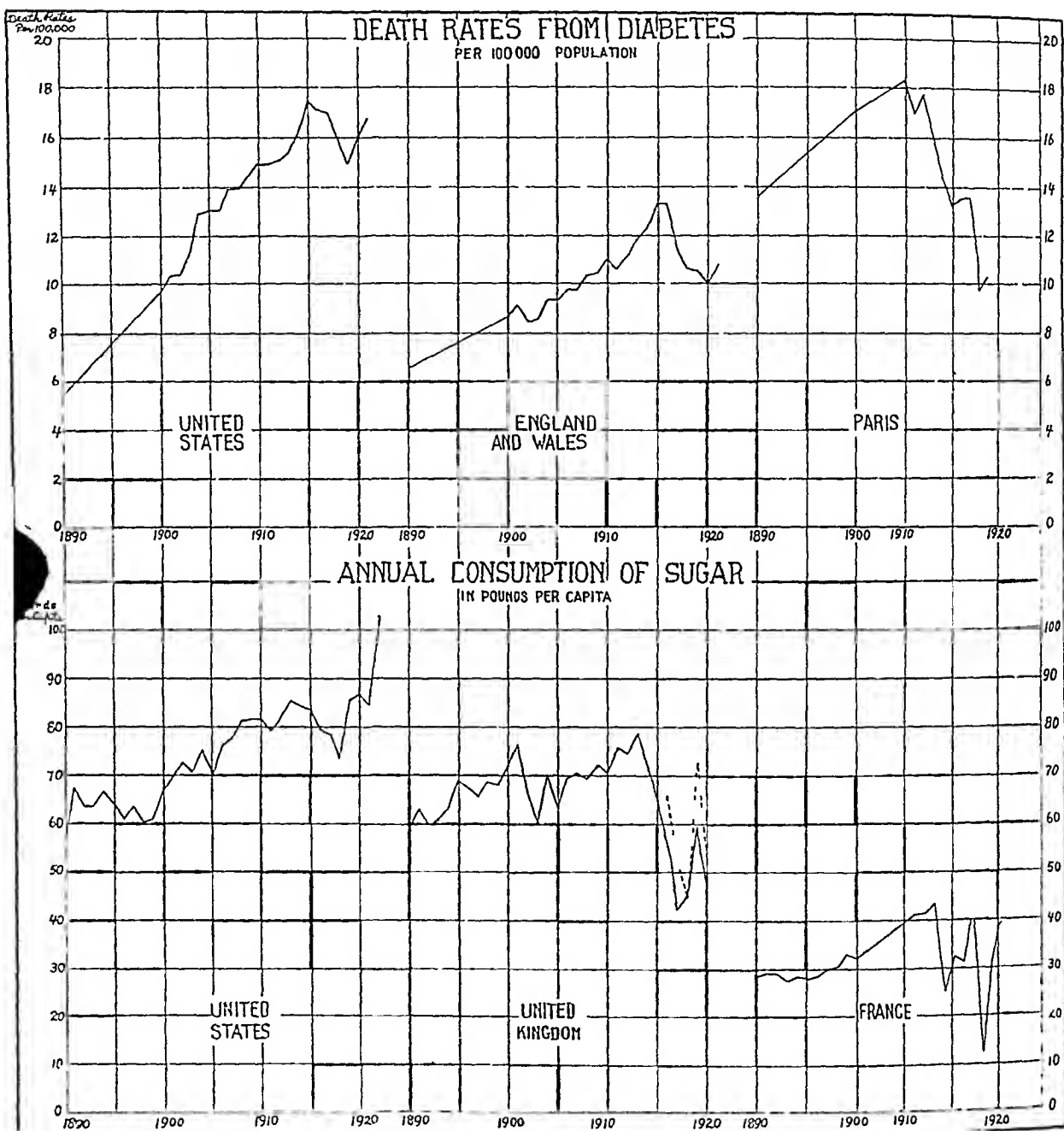


Chart 10—The estimated per capita consumption for sugar for certain years in the United States, Great Britain and France, and the diabetes death rates for the United States, Great Britain and Paris for the same years

<sup>21</sup> Tables of sugar consumption are based on various government and trade reports, including Yearbook of U S Department of Agriculture, General Statistics of France, International Sugar Trade Journal, Concerning Sugar by Palmer, and Licht's reports

TABLE 38—*Sugar Consumption in Relation to the Diabetes Death Rates in United States*

Year	Diabetes Death Rate* per 100,000	Sugar Consumption in Pounds per Capita	Year	Diabetes Death Rate* per 100,000	Sugar Consumption in Pounds per Capita
1890	5.5	54.46	1907	13.9	77.54
1891		67.46	1908	13.9	81.17
1892		63.76	1909	14.4	81.80
1893		63.83	1910	14.9	81.60
1894		66.64	1911	14.9	79.20
1895		64.23	1912	15.0	81.30
1896		60.90	1913	15.3	85.40
1897		63.50	1914	16.2	84.29
1898		60.30	1915	17.5	83.83
1899		61.00	1916	17.1	79.34
1900	9.7	66.60	1917	17.0	78.58
1901	10.3	69.70	1918	15.9	73.36
1902	10.4	72.80	1919	14.9	85.43
1903	11.3	70.90	1920	16.1	86.56
1904	12.9	75.30	1921	16.8	84.47
1905	13.0	70.50	1922		103.18
1906	13.0	76.10			

\* Diabetes death rates from Joslin. Rate for 1890 is for census year, others for calendar year.

TABLE 39—*Sugar Consumption in Relation to Diabetes Death Rate in Great Britain*

Year	Diabetes Death Rate* per 100,000	Sugar Consumption in Pounds per Capita	Year	Diabetes Death Rate* per 100,000	Sugar Consumption in Pounds per Capita
1890	6.5	58.89	1906	9.7	69.35
1891		63.00	1907	9.7	70.76
1892		59.60	1908	10.3	69.49
1893		60.88	1909	10.4	72.40
1894		63.16	1910	11.0	70.20
1895		63.85	1911	10.6	75.93
1896		67.07	1912	11.1	74.69
1897		65.19	1913	11.8	78.53
1898		68.74	1914	12.2	72.36
1899		68.42	1915	13.2	65.26
1900	8.6	71.60	1916	13.2	56.38
1901	9.1	76.33	1917	11.3	42.11
1902	8.4	66.47	1918	10.6	45.70
1903	8.5	60.29	1919	10.5	59.64
1904	9.3	70.35	1920	10.0	45.04
1905	9.3	63.34	1921	10.8	

\* Diabetic rates from Joslin for England and Wales.

TABLE 40—*Sugar Consumption in Relation to the Diabetes Death Rate in France*

Year	Diabetes Death Rate per 100,000, Paris	Sugar Consumption in Pounds per Capita, France	Year	Diabetes Death Rate per 100,000, Paris	Sugar Consumption in Pounds per Capita, France
1890	13.5	28.9	1910	18.4	40.11
1891		29.46	1911	16.9	41.09
1892		29.28	1912	17.7	41.48
1893		27.80	1913	16.0	43.84
1894		28.62	1914	14.3	25.86
1895		28.20	1915	13.2	32.83
1896		28.80	1916	13.4	31.63
1897		30.09	1917	13.5	41.07
1898		30.57	1918	9.6	13.28
1899		33.34	1919	10.3	31.11
1900	17.0	32.49	1920		39.28

It is apparent that rises and falls in the sugar consumption are followed with fair regularity within a few months by similar rises and falls in the death rates from diabetes, the changes during the period of the World War being particularly striking. If we had the death rate for diabetes of France as we have for the United States and Great Britain we should in all probability find a lower rate than prevailed in the latter countries, as the high rate of Paris is not so high as the rates have been over the same period for New York and London. The Paris rates are used because they are the only ones available for comparison with the sugar consumption of France, since it is the practice of the office of vital statistics of France to include diabetes in a group of general diseases in an abbreviated classification of causes of deaths under thirty-eight titles, instead of publishing by age, sex and cause, reports of deaths for the country as a whole for the 189 titles as is usual in England and the United States.

Riesman<sup>22</sup> after pointing out the fact that urine tests have changed so little in the last twenty to thirty years that greater accuracy in diagnosis of diabetes has probably not occurred during that time, expresses his opinion that the cause of the true increase of diabetes is the greater per capita sugar consumption, coupled with the increase of sedentary habits among most classes of people.

Joslin has given the impression in discussion of the substance of this paper that the increase in the per capita consumption of sugar in the United States can be discounted as a probable factor in the increase of diabetes death rates because of a presumed reduction in the per capita annual consumption of apples. Even if he can offer satisfactory evidence that there has been a bona fide reduction in apple consumption during the period of rising use of sugar, he would still have to meet the facts which Taylor mentions that there has been coincident with the reduction of per capita use of meat an increase in the use of fruits. Many other fruits besides apples carry a high sucrose content, and there is much evidence to show that increase in use of fruits (whether apples or not) has occurred over the same years which have seen the remarkable increase in sugar consumption above referred to.

#### SUMMARY AND CONCLUSIONS

The increase in the incidence and death rate from diabetes in the United States, and in New York City in particular, has been more rapid than that of any other disease for which we have records in the last fifty years.

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<sup>22</sup> Riesman, D. Quoted by Forsheimer, 1914, p. 718.

This increase, while it has affected all ages to some degree, has been most marked among women at all ages and among both men and women over 35 years of age in particular

There are wide variations in the susceptibility to diabetes, or at least in their ability to survive when it develops in them, among persons of different races, those of Semitic stock showing consistently the highest death rates and those of the Negro race in the United States the lowest

It is not at all clear that these marked differences in the death rates from diabetes in the people of various races are of fundamental biologic significance, since many elements of occupation, economic status, dietetic habits, etc., may be found sufficient to explain the range of experience with what may fairly be considered a disease of a fatigued function in the great majority of cases

Although the relative rarity of diabetes among rural workers and those engaged in hard manual labor or trades would appear significant, the lack of a thoroughly satisfactory basis for calculating death rates by occupational groups in this country deprives the contrasting picture, of high rates among desk workers and others engaged chiefly in mental rather than physical processes for their living, of much of its force

Seasonal variations in death rates, calculated on a monthly basis, are marked and apparently significant. Whether temperature and other accompanying weather conditions are responsible, or the similar seasonal incidence of infections, usually accompanied by fever and interference with nutrition and deteriorated bodily resistance, cannot be stated on the basis of present information

Geographical distribution of the disease as measured by death rates in the United States appears to be explicable on the basis of differences in the age grouping, race, economic status, and occupation of the people, high rates being found where there is a high proportion of the population in the later decades of life, after 45, where there are many Jews and where per capita wealth is high. Where life expectancy is high there is a lower diabetes death rate than in states where life expectancy is low, but this is probably due to the fact that the low expectancy states are those with a high proportion of Negroes in the population

The changes in food habits in the United States have probably contributed to the increase of diabetes, the higher carbohydrate element and greater abundance or superalimentation being believed to be a cause of overfatiguing the function of sugar tolerance

It is considered of much importance that educational measures be instituted to inform the public through medical and public health channels of the seriousness of the situation, and of the necessity of adjustment of food intake to exercise and vice versa

Moderation in the use of food and sufficient exercise with the entire body to justify the food absorbed, are important rules of hygiene for other reasons besides that of the relationship between obesity and diabetes, but if there were no other excuse for bringing this ancient teaching to people's attention, the greatly increased frequency of diabetes as a cause of sickness and death would alone seem to justify physicians and all those dealing with health and its protection in initiating and pushing vigorously a campaign of information in this subject

#### ABSTRACT OF DISCUSSION

DR LOUIS I DUBLIN, New York Dr Emerson is to be commended not only for bringing together for us these very interesting facts in regard to diabetes, but especially for his effort in utilizing a method which has rarely been used in the study of any of the degenerative diseases As he pointed out, the method of the epidemiologist and the vital statistician has been used in the study of the communicable diseases, in tracing the causes and the inter-relations of disease but rarely in such diseases as diabetes, nephritis, heart disease and the others where obviously we are not concerned with an infective organism The value of this new method is not only in giving us a glimpse into the natural history of the particular disease, but also in permitting us to make comparisons and in finding those diseases which are of a similar character You will remember that he showed that diabetes had a heavy incidence among females, a heavier incidence among whites than among the colored, that it had a very definite racial incidence, particularly among the Jews and Irish If you begin to look for other diseases that show similar characteristics you soon find them Take a disease like exophthalmic goiter, for example, it has these very characteristics, heavier incidence among females than males, heavier among whites than among colored and a special incidence among certain stocks Addison's disease is another I might list two or three others which show exactly these same relations It is clear that we are concerned here with a group of diseases that have a similar origin We are concerned in diabetes, exophthalmic goiter and Addison's disease with disorders of endocrine function, and no wonder we get the same kind of a picture when we plot the incidence of these diseases in this way

It is true that diabetes has increased rapidly in recent years It has increased more rapidly, however, in certain areas than in others It has increased in those areas where people who are more inclined to diabetes live The enormous increase in the city of New York is obviously due to the large increase in the number of Jews in that community, also in the number of Irish I may say, also, that there are a number of phenomena in this disease which future research will have to clear up Here and there in the study of the figures for localized areas we encounter conditions which are very difficult to explain on any theory While it is true that very generally the colored race has a low incidence compared to the white race, there are states in the South in which the condition is reversed and that is especially true of the urban populations In studying the figures for insured lives in the Metropolitan Insurance Company, we are struck with the fact that in certain southern communities in which the number of negroes is very large, the rates are higher for the colored than for the whites, but just why, I do not know

Finally, I would call attention to the fact that during the last year and a half, in fact, since the beginning of the very general use of insulin, the marked increase in the diabetes death rate seems to have come to a stop I am the last one to draw conclusions from a solitary and isolated fact like this covering a very short period I would call attention, however, to the fact that during the last twenty years, the death rate from diabetes has mounted as no other

condition. It has jumped a number of points a year. Certainly when this disease suddenly stops rising and begins to fall month by month and falls more rapidly with advancing time, it is suggestive that the increased use of insulin may be producing this result. It looks like a remarkable illustration of the efficiency of the new therapeutic agent.

DR EUGENE L. FISK, New York. Dr. Emerson has shown us a wonderful exposition of the fact that diabetes is something more than a cloud as big as a man's hand on the civilized horizon. While we are urging immunization against typhoid and vaccination against smallpox and measures of that sort we might well urge with more emphasis not only the periodic examination of the urine, but blood sugar tests, especially in middle aged people who tend to overweight, that is, the type of person who has been hinted at as the one most likely to have this trouble. I can give you a single instance of a tragic result from not following such custom—a sign of warning not to rely too much on the routine examination of the urine alone. A middle aged man, about 30 pounds overweight, showed a trace of albumin and a few hyaline casts in his urine, but no sugar. He was warned about these conditions, and advised to have the urine examined periodically, in addition, he was urged to have blood sugar examinations made, a warning he ignored. He got no encouragement from his physician to have that done as he had no sugar in the urine. That man died within eighteen months of diabetes. Now one death of that kind in a group of that sort is one death too many and I think health officers and others could with just as much reason urge functional tests of kidneys and blood tests to aid in checking inroads of disease like this as to advise vaccination, the Schick test and other measures commonly employed to combat communicable diseases.

DR ISAAC I. LEMANN, New Orleans. While there is less diabetes among the negroes than among whites, it is probable that the same cause that is operating to increase the diabetes among the whites is operating to exactly the same extent to increase diabetes among the negroes. I have compiled statistics from the Charity Hospital of New Orleans during two decades, from 1900 to 1910 and from 1910 to 1920. While the negroes contributed in this period somewhat less than one-half of the total admissions of the hospital, they contributed something less than their share of diabetes. Their share of diabetes was about one-third less than would have been expected as based on their proportion of admissions. That was true of both periods. When we compared the total incidence of diabetes in the two periods we found that it had gone up very markedly. We found, also, that the rate at which it had increased was exactly the same in the negroes as in the whites. So that we draw the conclusion that the same conditions were operating to increase it in the two races. It is worth while to note in this connection that there is nothing in the statistics to bear out the suggestion of Warthin that syphilis plays a rôle in the production of diabetes, for the negroes in these groups contributed a very much larger share of the syphilitic diseases, as everybody knows, but exhibited a less share of diabetes.

DR HAVEN EMERSON, New York. In considering the reduction in the diabetes death rate during 1923 and the first quarter of 1924 in New York, it is worth while to bear in mind that similar and quite as extensive drops in the rate have occurred as shown in the chart already presented, particularly in 1890 and during and after the influenza epidemic and food restriction periods of 1917 to 1919. Although it is possible that insulin is the main factor in the reduction of diabetes death rates in the last eighteen months, in this city and elsewhere in the United States, we cannot be sure of this until the reduction has continued for a considerably longer period. With regard to the effect of overliberal diets in causing diabetes, I must call your attention to the fact that while in the United States 150 pounds of meat is used per capita per annum, the people of Australia use 250 pounds per capita and the discrepancy between these two is made up in the United States chiefly by increased per



capita consumption of sugar, cereals, milk, vegetables and fruits. It would appear to me that evidence presented in my report supports the contention of Allen to the effect that much diabetes, among the wealthy in particular, is due to a fatigue of the function of carbohydrate tolerance by an attempt to assimilate a diet which overstrains this function. Apparently, among the reasons for the low rate among negroes is the fact that their occupations involve chiefly the use of the heavy muscles of the trunk and legs and arms, whereas the occupations of those among whom diabetes is most common involve the least physical effort.

# THE ASSOCIATION OF HYPERTENSION WITH SUPRARENAL TUMORS

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That tumors of the suprarenal gland may be associated with hypertension was first pointed out by Edmund Neusser<sup>1</sup>. He observed two patients in whom the condition ran the typical clinical course of nephritis with hypertension, but at necropsy the kidneys and arteries were found not affected, the pathologic finding in each instance being a neoplasm of the suprarenal gland, described as a carcinoma by Neusser. These observations attracted little attention till Vaquez,<sup>2</sup> influenced by Josue's discovery of the vascular lesions produced by epinephrin, formulated the doctrine that arterial hypertension is due to hyperepinephrinemia. It was shown that diffuse hyperplasia and circumscribed adenoma formation in the suprarenal cortex are exceedingly common in persons suffering from hypertension, whether it is nephritic or what is now termed "essential" hypertension. Thus Aubertin and Ambard<sup>3</sup> found that out of eight cases of hypertension four showed diffuse cortical hyperplasia and three others adenomas of the suprarenal cortex, in only one instance was the gland normal. Philpot<sup>4</sup> found that the weight of the suprarenals is much greater in sufferers from chronic nephritis than in comparable material of the same age group without nephritis. In a series of thirty cases of hypertension one of us found cortical adenomas present in five instances, while in fifty successive necropsies in which no hypertension had been present, adenomas were found in only one case (and even in this solitary instance the kidneys were granular).

It is thus seen that there is considerable anatomic evidence that hyperplasia of the suprarenal glands is a frequent concomitant of arterial hypertension. Unfortunately, the functional interpretation of these changes in the suprarenals presents a very difficult problem. In most instances the hyperplasia noted has involved the cortex, though a few authors (Wiesel,<sup>5</sup> Parkinson,<sup>6</sup> etc.) have observed enlargement of the

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\* From the Medical Division of the Montefiore Hospital

† Read before the American Society for Clinical Investigation, May 5, 1924

1 Neusser. Nothnagel's *Spezielle Pathologie und Therapie*, Vienna, **18** 71, 1898

2 Vaquez. *Tr Cong franç de méd*, 1904, p 338

3 Aubertin and Ambard. *Bull ét mém Soc med d hôp de Paris* **21** 175, 1904

4 Philpot. *Quart J Med* **3** 34, 1909

5 Wiesel. *Verhandl d Kongress f inn Med* 1907, p 221

6 Parkinson. *Tr Path Soc London*, **58** 187, 1907

medulla, which is rather what one would expect if the hypertension is to be attributed solely to a hyperepinephrinemia. Despite the initial, seemingly successful, experiments of Schur and Wiesel,<sup>7</sup> using a technic that has not withstood criticism, an increase in the epinephrin content of the blood has never been proved to exist in patients suffering from hypertension. In fact even the presence of epinephrin in the general circulation has not been demonstrated unequivocally, though exceedingly delicate biologic reactions have been applied. Schmorl's<sup>8</sup> analyses of suprarenal glands from hypertensive subjects did not show them to contain more epinephrin than do the suprarenals of persons with a normal arterial tension.

In view of the well known action of epinephrin in mobilizing hepatic glycogen, it might well be supposed that one of the manifestations of an increased epinephrin content of the blood would be hyperglycemia. In accordance with this, Neubauer<sup>9</sup> was the first investigator to show that the blood sugar is usually increased in hypertensive subjects, and this has been confirmed by most subsequent investigators, particularly in vascular (essential) hypertension.

The table summarizes our findings in eleven patients presenting hypertension in whom blood sugar determinations were made, and who subsequently came to necropsy.

*Blood Sugar Findings in Eleven Patients with Hypertension*

Number	Blood Pressure	Blood Sugar (Mg per 100 C c)	Pancreatic Arterioles
1	204/100	150	Markedly thickened
2	220/160	156	Normal
3	180/110	110	Normal
4	180/135	132	Slightly thickened
5	208/132	122	Normal
6	210/94	152*	Markedly thickened
7	220/140	95	Markedly thickened
8	170/100	142*	Slightly thickened
9	240/150	134	Moderately thickened
10	225/100	130	Thickened
11	210/118	151	Slightly thickened

\* Glycosuria

The foregoing determinations of the blood sugar were made by the method of Folin and Wu, with which the normal values range below 120 mg per hundred cubic centimeters. It is seen that in eight of the eleven cases the blood sugar is definitely above the normal, while in one of the remaining three instances it is at the upper limit of the normal. In two of the patients the blood sugar exceeded the renal threshold with resulting glycosuria. But in no case was the blood sugar level as high as is usually seen in true (pancreatic) diabetic

7 Schur and Wiesel. *Wien klin Wchnschr* 20 699 1907

8 Ingier and Schmorl. *Deutsch Arch f klin Med* 104 262, 1911

9 Neubauer. *Biochem Ztschr* 25 284, 1910

patients on an unrestricted diet, though Hitzenberger and Richter-Quittner<sup>10</sup> of Falta's clinic have reported such high values in patients with hypertension Schwab,<sup>11</sup> the results of whose determinations agree with ours, explains the high readings of these authors by the technic that they employed A study of the table reveals no close parallelism between the height of the glycemia and the blood pressure

Pancreatic arteriosclerosis of more or less marked severity was present in eight of the eleven cases listed in the table Here again there seems to be no close correlation between the degree of the hyperglycemia and the severity of the vascular changes In fact, the lowest blood sugar reading recorded was in a patient with extremely severe sclerosis of the pancreatic arterioles It is common to see at necropsy severe sclerosis of the pancreatic vessels where no hyperglycemia existed during life, but it should be borne in mind that the arteriosclerosis of the larger arteries as seen macroscopically is very different in its consequences for the parenchyma of the organ than the arteriosclerosis of the finer arterial radicals to which we refer in the table The fact that the the hyperglycemia does not attain any great height, despite the long continued lack of dietary control, seems also to differentiate it from the ordinary pancreatic hyperglycemia Nevertheless, in view of the comparative frequency of pancreatic arteriosclerosis in hypertonic subjects, it does not seem justifiable without further evidence to attribute the increased blood sugar to a heightened secretion of epinephrin, though this is certainly a strong possibility

It is thus seen that neither experimental evidence nor chemical and pharmacologic study of the blood lend much support to the attractive hypothesis ("beautiful dream," as the late T C Janeway<sup>12</sup> called it) of an excessive epinephrin content of the blood in hypertension It is our aim in the present communication to point out that in certain, though rare, instances neoplasms of the suprarenal gland produce chronic arterial hypertension

#### TUMORS DERIVED FROM THE SUPRARENAL MEDULLA

In accordance with the development of the medulla from the formative cells of the sympathetic ganglions, three varieties of tumors have been found

- 1 Sympathoblastomas, made up of immature sympathoblasts
- 2 Ganglioneuromas, consisting of relatively mature sympathetic ganglion cells, in which differentiation has gone further than in the tumors of Group 1

<sup>10</sup> Hitzenberger, K., and Richter-Quittner *Wien Arch f inn Med* 2 2, 1921

<sup>11</sup> Schwab *Virchows Arch f path Anat* 242 1, 1923

<sup>12</sup> Janeway *Am J M Sc* 145 638, 1913

3 Paragangliomas (pheochromocytomas, L. Pick), made up of apparently mature chromaffin cells

Only in connection with the rare paragangliomas (chromaffin tumors) has hypertension been reported. In the literature we have found the following five cases of paragangliomas with adequate blood pressure observations or the anatomical equivalent of hypertension (cardiac hypertrophy in the absence of all renal, arteriolar, valvular or other lesions which might cause hypertrophy)

1 Orth<sup>13</sup> found at necropsy a case in which the intra vitam diagnosis was chronic nephritis (blood pressure, 220 systolic, 140 diastolic). At the necropsy the kidneys and arterioles were normal but there was a paraganglioma of the suprarenal gland in which Orth was able to demonstrate, both microchemically and by biologic reactions, the presence of large amounts of epinephrin.

2 In a patient, aged 2½ years, with paraganglioma of the suprarenal, Wiesel<sup>14</sup> found very advanced arteriosclerosis with medial changes similar to those occurring after the experimental injection of epinephrin.

3 Bergstrand<sup>15</sup> found a suprarenal paraganglioma in a patient presenting large cardiac hypertrophy (weight of heart 500 gm) with no renal, arterial or valvular lesions.

4 Labbe, Tinel and Doumer<sup>16</sup> observed a woman, aged 28, whose blood pressure varied greatly, though it was nearly always very high. During some of the paroxysms of hypertension the blood pressure was as high as 280 systolic and 190 diastolic. At times it was as low as 120 systolic, and 80 diastolic. Tremendous fluctuations occurred in the course of the same day. During the paroxysms of extreme hypertension, the patient presented signs of peripheral vasoconstriction, such as pallor and coldness of the extremities. There were evidences of sympathotonia, tachycardia, mydriasis, etc. At times the urea nitrogen of the blood was very high, but later this became normal. The symptoms lasted for several months, till they finally terminated in acute pulmonary edema. The sole cause for the hypertension revealed by the necropsy was a paraganglioma of the suprarenal. The only lesions found in the kidneys were some interstitial hemorrhages and a number of foci of coagulation necrosis of the tubular epithelium, which the authors considered as due to the ischemia resulting from intense vasoconstriction. The heart weighed but 340 gm.

5 In contradistinction to these observations, Thomas<sup>17</sup> examined a case of paraganglioma of the suprarenal in which there was no evi-

13 Orth. Sitzungb. d. k.-Preussischen Akad. d. Wissensch. **11** 34, 1914.

14 Wiesel. Der heutige Stand der Lehre von der Arteriosclerose, Vienna, 1909.

15 Bergstrand. Hygeia, Stockholm **82** 321, 1909.

16 Labbe, M., Tinel, J. and Doumer. Bull. et mem. Soc. méd. d. hop. de Paris **46** 982 (June) 1922.

17 Thomas. Frankfurt Ztschr. f. Path. **16** 376, 1915.

dence of hypertension. However, the patient, aged 80 years, was seen only terminally. It is quite possible that senile cachexia prevented the development of cardiac hypertrophy and hypertension, as it occasionally does in chronic nephritis.

There are numerous cases of ganglioneuroma and a few of sympathoblastoma of the suprarenal recorded in the literature, but none show any evidence of hypertension. Nor does hypertension occur when tumor metastases are present in the suprarenals. Evidently, then, only the paragangliomas among the tumors of the suprarenal medulla may be accompanied by hypertension, as in four of the five instances recorded in the foregoing.

#### TUMORS DERIVED FROM THE SUPRARENAL CORTEX

We have noted in the foregoing the frequent finding of diffuse and circumscribed (adenomatous) hyperplasia of the suprarenal cortex in cases of hypertension. Also before mentioned were the difficulties encountered in interpreting the statistically evident correlation between the cortical hyperplasia and the increased blood pressure. Does the diffuse or nodular cortical enlargement bear a causal relationship to the hypertension, is it merely a reaction of the cortical cells to products of renal retention (the work of the Aschoff school has shown that the suprarenal cortex has an important detoxifying function), or is it the result of the arteriosclerosis found in the vast majority of cases of hypertension? Whichever of these explanations is correct for the ordinary cortical hyperplasias, there are in the literature the following few instances in which there seems little reason to doubt the causal connection of a tumor of the suprarenal cortex and the hypertension in the particular case.

1 Bland-Sutton<sup>18</sup> reports a case of tumor of the suprarenal cortex, in which there was enormous cardiac hypertrophy for which he could find no other cause.

2 Bullock and Sequeira<sup>19</sup> observed a child, aged 11 years, who was fully matured sexually and had hypertension, at necropsy a tumor of the suprarenal gland was found, with the morphology of the cortex.

3 and 4 The two cases of Neusser,<sup>1</sup> before mentioned, belong to this group.

5 and 6 Of very great interest are two cases observed by Volhard,<sup>20</sup> in which the clinical picture was that of diffuse nephritis with hypertension and albuminuria. In each instance after operative removal of a hypernephroma the hypertension disappeared.

18 Bland-Sutton, J. Brit. M. J. **2** 593, 1918.

19 Bullock and Sequeira. Tr. Path. Soc. London, **56** 189, 1905.

20 Volhard. Mohr and Staehelin's Handbuch der inneren Medizin, Berlin, **3** 1291, 1918.

7 Mackintosh<sup>21</sup> observed a boy, aged 14 years, presenting obesity, hirsuties of forehead, eyebrows, chin, axilla and pubis. Striae atrophicae were present on the abdomen. Glycosuria was found. The blood pressure was 240 systolic, 170 diastolic. The left lower ribs bulged and the author considered the case one of suprarenal hyperplasia. (Note the minute resemblance to our Case 2 reported further.)

8 Hoag<sup>22</sup> communicated the following exceedingly interesting case, with a necropsy report by Waithin. A girl, aged 4 years, had precocious sexual development. The blood pressure ranged from 160 to 145 systolic, and from 100 to 90 diastolic, a tremendous hypertension for a child of that age. Necropsy revealed a hypernephroma and arteriosclerosis of the pial vessels.

9 Mathias<sup>23</sup> reports the case of a girl, who, at the age of 3 years, was sexually mature and had a well marked beard. She died at the age of 18, the necropsy revealing a hypernephroma, as well as marked hypertrophy of the left ventricle. No blood pressure readings are recorded, but the necropsy protocol reveals no cause for the cardiac hypertrophy in the kidneys, arterioles or valves of the heart.

We have recently had the opportunity of studying the following case, in which the pathogenetic role of the suprarenal tumor seems unequivocal.

CASE 1—M. F., a man, aged 24, was admitted Jan. 11, 1923, complaining of dyspnea on exertion and palpitation, both symptoms being only of three months duration.

The family history was irrelevant. The patient denied having any previous illness.

About three months prior to his admission to the hospital, the patient began to experience palpitation and dyspnea on exertion, which grew progressively worse. He also complained of precordial pain, without well defined radiation. Shortly before admission the patient began to have a dry cough and noted a pain in the right axilla.

The patient's replies indicated mental deficiency.

*Physical Examination*—A well developed and well nourished young man, breathing rapidly and with obvious effort was seen. He was not cyanotic. The prominent supraorbital ridges, heavy jaw, large hands and feet, and thick eyebrows meeting in the midline gave the patient an acromegalic appearance.

The head and neck organs presented no significant deviations from the normal.

*Lungs*—Slight impairment at right base posteriorly. A few râles were heard at both bases.

*Heart*—The somewhat diffuse apex beat was felt in the sixth interspace, outside the nipple line. Percussion revealed that the heart was enlarged to either side, the left border being 14 cm. from the midline in the sixth interspace and the right border 5 cm. from the midline in the fourth interspace.

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21 Mackintosh, Ashley. *Quart. J. Med.* **14**. "Proceedings," following p. 308, 1920.

22 Hoag, Lynne. Malignant Hypernephroma in Children, *Am. J. Dis. Child.* **25** 441 (June) 1923.

23 Mathias. *Virchows Arch. f. path. Anat.* **236** 446, 1922.

The sounds at the apex were fairly loud, a presystolic gallop rhythm was heard here. The second sound was accentuated at the aortic area. A short systolic murmur was audible at the base.

*Pulse*—The radial artery felt thickened. The tension was high, but alternate beats felt weaker. The blood pressure was 200 systolic, and 150 diastolic. The presence of the pulsus alternans was proved by the manometric readings, and by polygraphic tracings.

Examination of the abdomen, extremities, genitalia, lymph nodes, and reflexes revealed no abnormalities.

The blood examination disclosed a slight secondary anemia.

*Urine*—Spontaneous concentration was 1025. Albumin was usually present, sometimes in considerable quantities. On most examinations casts were absent; occasionally some hyaline and granular casts were found. White blood cells were usually present, but never any erythrocytes.

*Blood Chemistry*—The following were the results expressed in milligrams per hundred cubic centimeters.

Date	1/13	1/20	2/10	2/21	3/2	3/21*
Urea nitrogen	22.4	14.0	18.2	24.9	11.0	11.9
Nonprotein nitrogen	50.2	34.1	30.7			
Uric acid	2.5	2.7	2.1	6.0	2.1	
Creatinin	1.2	1.3	0.9			
Sugar				156.0		106.0
Cholesterol					206.0	

\* Six days before death.

Phenolphthalein elimination 50 per cent (after intramuscular injection), on two occasions.

*Fundus Oculi*—Right eye. The nerve head was red, its margins indistinct. The veins were engorged, the arterioles extremely narrow and in places lost. There was perivascularitis. The left eye was the same as the right eye but there were numerous fine spots of degeneration between the nerve head and macula, and a few spots of fibrinous exudate above and to the dorsal side of the nerve head. Diagnosis. Albuminuric retinitis, arteriosclerosis (?).

Blood Wassermann was negative.

*Electrocardiogram*—T was inverted in Leads I and II and small in Lead III. R showed distinct slurring.

The sella turcica was rather large and shallow in the stereorocntgcnoqram.

During the patient's stay in the Mt. Sinai and Montefiore Hospitals he continued to suffer from dyspnea, palpitation and other evidences of myocardial insufficiency. The blood pressure remained around 220 systolic, 160 diastolic, and the alternation of the pulse persisted.

March 7, the patient showed signs and symptoms of bronchopneumonia. His condition gradually grew worse, he became delirious and died March 27. The total time that elapsed between the onset of symptoms and death was less than six months.

In view of the hypertension in the absence of any evidence of renal insufficiency, or even of renal involvement other than chronic passive congestion, a diagnosis was made of vascular (essential) hypertension with secondary myocardial insufficiency.

*Necropsy*—The head and neck organs were negative (the retina was not examined).

*Heart*—Enormously hypertrophied and dilated, and weighed 880 gm. Hypertrophy was most marked in the left ventricle, the walls of which measured 22 mm in thickness. The heart muscle was slightly fatty. Aside from slight atherosclerotic patches on the mitral and aortic cusps, the valves were normal. The coronary arteries showed a few fatty flecks but everywhere were smooth.



and patent. The aorta was normal, only a few small fatty areas around the mouths of the branches being seen. The larger vessels throughout the body appeared normal, though the vessels forming the circle of Willis felt thicker than usual.

*Lungs*—Bilateral bronchopneumonia and edema.

The kidneys together weighed 320 gm. The capsule stripped with some difficulty, revealing a slightly irregular, reddish-brown surface on which there were some yellowish flecks. The markings were somewhat blurred. The larger renal vessels were slightly thickened. In the cortex of the right kidney was an organized infarct.

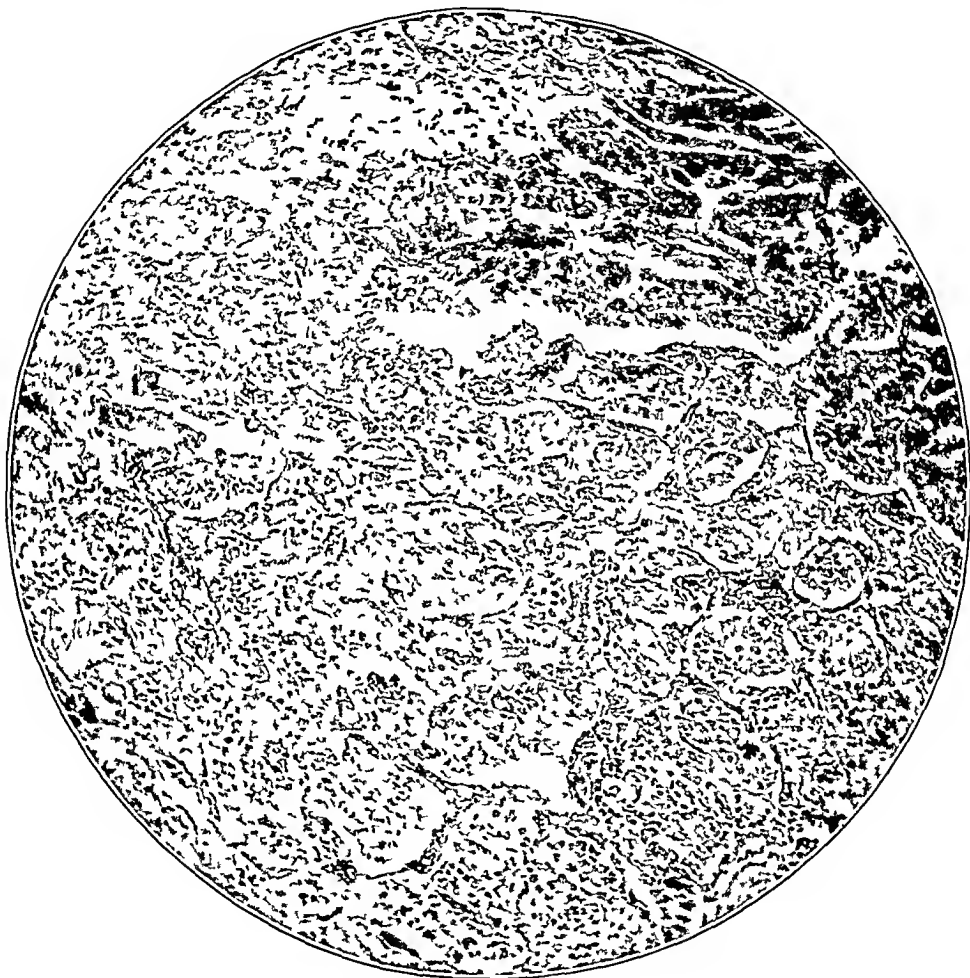


Fig 1—Photomicrograph of section of tumor of the left suprarenal gland (Case 1). Cells arranged in alveoli, septums consist of capillaries filled with blood (low power).

Microscopically, congestion was immediately evident, many of the glomerular loops as well as the intertubular capillaries being distended with blood. The finest arterioles (vasa afferentia to the glomeruli) showed no evidence of arteriosclerosis, either in the hematoxylin-eosin, Mallory or elastin (Weigert) preparations. A few of the larger arterioles (arcuate and interlobular vessels) showed distinct intimal thickening. The medial musculature of these arterioles appeared somewhat thicker than usual and in places the muscle cells stained poorly. Nearly all the glomeruli appeared normal aside from congestion. There was neither epithelial nor endothelial proliferation,

nor was there evidence of exudation into the glomerular capsules or tufts, the loops of the latter containing numerous red cells. There were a few minute foci of glomerular fibrosis, but their number was very small. Around one glomerulus was a moderate pericapsular fibrosis. Some of the tubules contained pink staining casts. A few of the convoluted tubules were dilated and lined by low epithelium. There was slight epithelial desquamation.

*Suprarenal Glands*—The right weighed 25 gm. It measured 6 by 4 by 2.5 cm. Nearly all of the gland was replaced by a large tumor mass involving both the cortex and medulla, only a small portion of normal tissue containing



Fig 2—Section from periphery of tumor of left suprarenal. Shows a typical proliferation of cells (high power)

both cortex and medulla was seen at one end. The tumor was soft, somewhat elastic and grayish in color, and contained yellow necrotic portions. The left suprarenal gland weighed 10 gm, and on section was seen to contain ten small cortical adenomas. Aside from the adenomas the cortex was hyperplastic.

Sections through the left suprarenal showed the adenomas to be of the usual structure, made up of cortical cells rich in lipoids and arranged in rather irregular fascicular formations. Sections of the large tumor of the right suprarenal revealed a different appearance. In places the resemblance to the cells and arrangement of the cortex was readily seen, elsewhere more atypical proliferation had occurred. The cells had either vesicular or deeply staining

nuclei and the cytoplasm of most cells stained uniformly pink, giving no evidence of high lipid content. The cells had an alveolar arrangement, but the septums in places contained little connective tissue, being composed almost entirely of well filled blood capillaries (Figs 1 and 2). There were extensive areas of necrosis, and here and there were the remains of hemorrhages. There were scattered phagocytic cells loaded with hemosiderin. It seems reasonable to believe that this larger mass originated from a cortical adenoma (struma suprarenalis of Virchow), which started to proliferate more vigorously and now gives a histologic picture resembling hypernephroma. The histogenesis was apparently quite analogous to the development of malignant growths from ordinary adenomas of the thyroid, which Marine believes to be the almost invariable starting point of thyroid carcinomas. No accessory suprarenal tissue was found along the spermatic cord or elsewhere.

The other organs presented no significant pathologic changes. The smaller arterioles in the various viscera were not thickened, except for slight hyalinization in some of the arterioles of the spleen.

The essential intravital and necropsy findings may be summarized as follows. A youthful patient presented a blood pressure of 220 mm of mercury<sup>24</sup> systolic, 160 diastolic, with great cardiac hypertrophy. There was no evidence of kidney disease. Renal function was totally intact, the urea nitrogen being 11.9 mg per hundred cubic centimeters of blood six days before death. At necropsy, tremendous cardiac hypertrophy (weight of heart 880 gm) was found. No valvular lesion was present. The renal lesions were slight, focal and not diffuse, and evidently secondary to the slight arteriolar lesions. It is to be emphasized that the latter were found in only a very few vessels, the large majority being normal. Almost all of the glomeruli were intact, and it is inconceivable that the hypertension could be attributed to the few fibrotic foci. The usual explanations of cardiac hypertrophy, valvular, diffuse renal or arteriolar lesions, fail us in this instance. But there was a tumor of the suprarenal cortex, and in the light of the findings of previous investigators detailed in the foregoing, there seems no reason to doubt a causal connection between the hypertension and the tumor of the suprarenal gland.

Parenthetically, we may call attention to the "albuminuric" retinitis, which the patient presented in the absence of renal insufficiency or hypercholesterolemia. The arteries of the fundus, as is usual in this condition, were very narrow in places lost. The occurrence of these changes in the eye-grounds in this case confirms the view of Volhard<sup>25</sup> that albuminuric retinitis is due to ischemia produced by a narrowing of the retinal arteries, and is not necessarily the consequence of retention of urinary constituents.

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<sup>24</sup> The exceedingly high diastolic pressure furnishes a measure of how great the peripheral resistance must have been. (See also the cases of Labbe, Tinel and Doumer and of Mackintosh.)

<sup>25</sup> Volhard. *Verhandl. d. deutsch. Gesellschaft f. inn. Med.* **33**: 422, 1921.

We add the following juvenile case, although unfortunately no necropsy was obtained. But the clinical picture was so characteristic of suprarenal hyperplasia as to leave little doubt of the diagnosis.

CASE 2—S. G., a girl, aged 12, was admitted to the Montefiore Hospital complaining of weakness and adiposity. Her family history contained no items

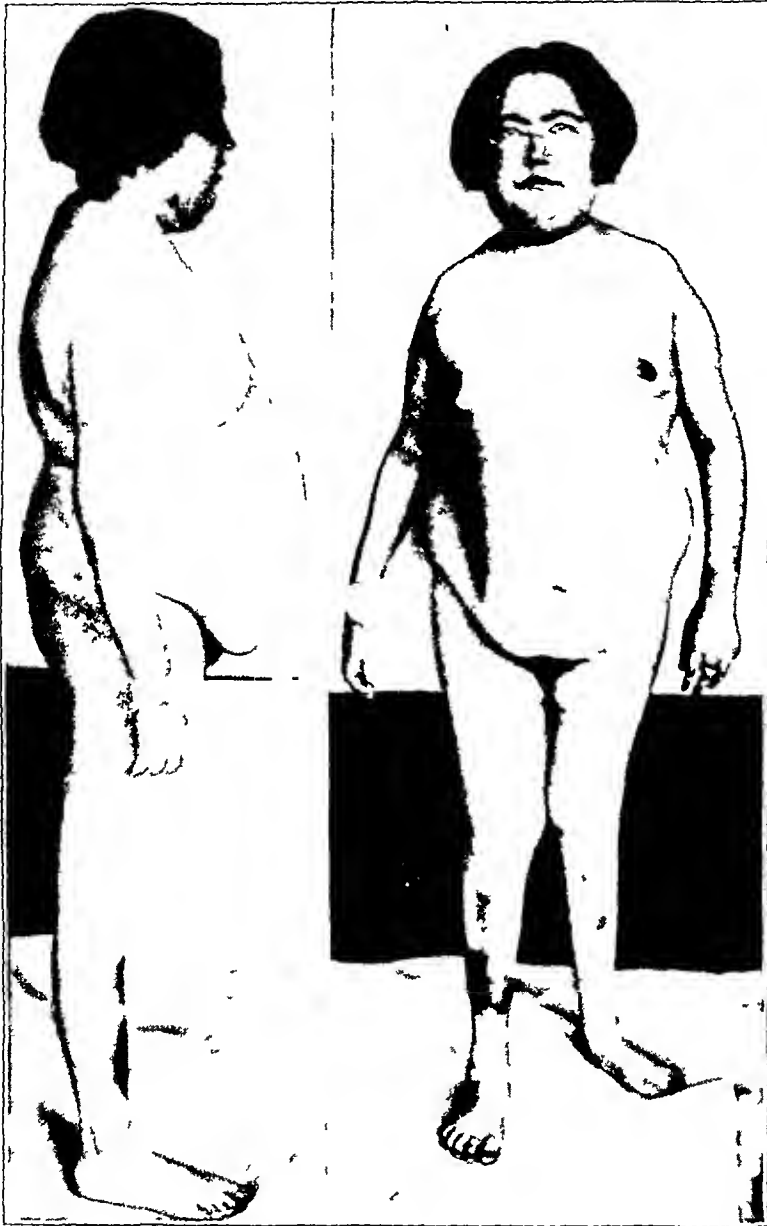


Fig. 3—Side and front view of Case 2, a girl, aged 12 years, showing pubertas precox, obesity, hirsuties of the chin, cheeks and eyebrows, striae atrophicae of abdominal wall, and the physique of an adult woman.

of interest. Between the ages of 9 months and 2 years the patient suffered from fainting spells. Strabismus was present since infancy. The patient underwent an operation for double cataract at the age of 5. About this time she had scarlet fever, complicated by pyelitis.

The present illness dated back seven years, when the patient was aged about 5½ years. She suddenly began to gain in weight and became disproportionately

adipose, gaining about 75 pounds (34 kg) in one year. She was seen by many physicians and treated symptomatically with various glandular preparations. About a year ago the parents noticed a change of skin coloration. The patient developed a tendency to fall asleep. A routine urine examination revealed 4 per cent of sugar. Polyuria and nocturia developed about this time. At the age of 11 hair began to grow on the face, axilla and pubis. The patient had never menstruated.

*Physical Examination*—An undersized child, appearing many years older than her actual age, was seen (Fig 3). She was exceedingly obese and had a very red, plethoric facies. There was a well marked growth of hair on the chin and lower cheeks. The pubic and axillary hair were well developed. On the abdomen were pigmented striae.

*Eyes*—Bilateral aphakia. Satisfactory examination of the fundus was impossible. The other head and neck organs were negative.

*Heart*—Enlarged to the left. The sounds were of good quality. The second sound was accentuated over the aortic area. There were no murmurs.

The blood pressure was 190 systolic, 130 diastolic.

*Skin*—There were abscesses on the back and neck, and a mycotic infection of the nails. There was no edema whatever. There were ulcers on the legs.

*Urine*—Spontaneous concentration to 1022. Sugar was present, but no acetone bodies. There was a heavy cloud of albumin. Microscopic examination revealed neither casts nor cellular elements. Phenolsulphonephthalein elimination, 45 per cent (after intravenous injection).

*Blood Chemistry*—Urea nitrogen, 11 mg, uric acid, 5 mg, sugar 260 mg per hundred cubic centimeters.

*Blood Count*—Erythrocytes, 4,500,000, leukocytes, 11,000, of which 78 per cent were polymorphonuclear, 16 per cent lymphocytes, 5 per cent monocytes, and 1 per cent eosinophils. Hemoglobin, 90 per cent (Sahli).

*Basal Metabolism*—Plus 1, minus 3 per cent.

Roentgenography revealed no changes in the sella turcica.

The patient was placed on an antidiabetic diet and digitalized. The urine rapidly became normal, the sugar and albumin disappearing completely. At one time signs and symptoms of bronchopneumonia appeared, but these cleared up. The abscesses of the neck and back healed and her parents insisted on removing the child from the hospital. We then lost sight of her, but recently obtained information that she had died three weeks after leaving the hospital.

#### SUMMARY

At the age of 5 years, a girl suddenly started to gain weight rapidly, taking on 75 pounds (34 kg) in a year. Glycosuria developed but the patient remained very fat. In addition to this she showed very markedly precocious development of the secondary sexual characteristics, though she did not menstruate. Also, a heterosexual growth of hair appeared on the cheeks and chin. In other words, she presented that combination of obesity and precocious sexual development which Parkes Weber has designated as "precocious obesity." The triad of sexual precocity (pubertas praecox), obesity and development of heterosexual virilism are practically pathognomonic of hyperplasia or tumor of the suprarenal cortex in young children, especially in girls, being differentiated from ovarian or pineal precocity by the heterosexual hair and from the adiposity of pituitary lesions (Froehlich's syndrome) by the sexual

precocity The twelve cases of pineal tumor causing precocity collected by Boehm<sup>26</sup> were all in boys, they usually have the classical symptoms of brain tumor

# COMMENT

Of interest to us in the present connection is the hypertension in the absence of any evidence of nephritis, the albuminuria present at one period disappearing on digitalization The patient was exceedingly plethoric, presenting the appearance seen in the essential hypertension of adults ("roten Hochdruck" of Volhard<sup>27</sup>), and quite a contrast to the pallor often seen in nephritic patients In general, extensive arteriosclerosis is exceedingly rare in a child, aged 12 years, moreover, in this patient none of the palpable vessels felt sclerosed Despite the unfortunate lack of anatomic confirmation, it seems justifiable to diagnose the presence of a hyperplasia or neoplasm of the suprarenal cortex in this case, and to attribute to this the otherwise inexplicable hypertension of a child, aged 12, not suffering from nephritis Whether the diabetes was merely coincidental or whether it was of suprarenal origin we are not in a position to say

From the two patients reported in the foregoing and the other confirmatory cases collated from the literature, it is seen that cases of hypertension occur in association with suprarenal tumors, particularly in youthful subjects In Case 1 we were able to demonstrate anatomically that there were no considerable lesions of the kidneys or arterioles which could be held responsible for the hypertension The two cases of Volhard before mentioned, in which hypertension disappeared after the removal of a hypernephroma, seem to prove that in these cases the hypertension was due to the tumor

The pathogenesis of the hypertension in cases of suprarenal tumor seems difficult of interpretation We have seen, that of the tumors of the medulla, only those composed of mature chromaffin cells, the paragangliomas, are accompanied by hypertension (in four out of the five published cases), while the primary sympathoblastomas and ganglioneuromas, as well as all metastatic growths, are unaccompanied by hypertension And while most tumors arising from the cortical cells are not associated with hypertension, we have cited and described the foregoing cases with exceedingly high blood pressure That it is not the destruction or irritation of the normal suprarenal tissue that is the cause of the hypertension is proved by the cases of Addison's disease due to metastatic neoplasms The simplest view would be to explain

26 Boehm, quoted by Collett, Arthur Genito-Suprarenal Syndrome (Suprarenal Virilism) in a Girl One and a Half Years Old, with Successful Operation, *Am J Dis Child* 27 219 (March) 1924

27 Volhard *Verhandl d deutsch Gesellsch f inn Med* 35 138, 1923

the high blood pressure by an increased secretion of epinephrin, but this does not offer an immediate explanation of the increased arterial tension in cases of cortical tumor. In the case of Addison's disease, it is uncertain whether the low blood pressure and other symptoms are due to the destruction of the cortex or of the medulla, possibly the Addisonian symptom complex is to be attributed to a functional insufficiency of the whole gland. The symptoms of the cases of suprarenal tumor before described are, in several fundamental characteristics, diametrically opposed to those of Addison's disease. Thus the latter is characterized by subnormal blood pressure and hypoglycemia, while in the cases of suprarenal tumor there is more apt to be hypertension and hyperglycemia. It seems probable that the hypertension found in some cases of suprarenal tumor is due to an excess production of the same substance, the lack of which produces the symptoms of Addison's disease.

#### CONCLUSIONS

Clinically, the instances of suprarenal neoplasm listed present the picture termed, as a confession of ignorance of the pathogenetic factor, essential hypertension (R. Schmidt), or, having in mind the usual outcome, presclerosis (Huchard). It has long been realized that these names merely place in a common rubric pathogenetically and etiologically heterogeneous groups of cases, having in common hypertension in the absence of evidence of renal involvement. The great interest of the cases of hypertension associated with suprarenal tumors lies in the demonstration that in certain instances (fifteen reported cases) of chronic non-nephritic hypertension the increased blood pressure is associated with an anatomically demonstrable lesion of the suprarenal gland, though the precise mechanism of the production of the hypertension remains unexplained. One small group of cases is thus removed from the great group of essential hypertension and may well be termed suprarenal hypertension.

# SYPHILITIC AORTIC INSUFFICIENCY \*

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Syphilis of the aortic orifice is now recognized as the most common cause of aortic insufficiency in adults. The disease is so frequently associated with syphilis of the aorta itself that from a pathologic standpoint, one is not justified in considering the two conditions separately. Indeed, whether the aortic leaflets are ever primarily and exclusively attacked by syphilis, true syphilitic endocarditis, is still an open question. This, as well as several other interesting problems presented by the disease can best be studied by correlating clinical and pathologic observations on a large series of patients. Although the group of cases here discussed is not large, certain facts were observed which may serve as a basis for further study of what may be called syphilitic cardio-aortic disease.

This paper is based on the clinical and pathologic studies of twenty-five patients, who with but two exceptions, were under my observation at Cleveland City Hospital during the last three years. No selection of patients was made, as the group studied included all but four cases of syphilitic aortic insufficiency seen at the hospital during this time. Twenty-four of the patients were men and one was a woman. The youngest was aged 30, the oldest 64 years, the average age for the group was 40 years. Eighteen were between 30 and 45 inclusive, while three were between 60 and 64. Fourteen were white and eleven were colored. All had the signs of aortic insufficiency and, with one exception, all died of heart failure. The diagnosis was confirmed by postmortem examination in all cases included in this series. Physical exertion did not appear to be a determining factor in the heart failure, since at one extreme were laborers, at the other, a minister, a musician and a chauffeur, in a somewhat intermediate position a chiropractor.

## SYMPTOMS AND CLINICAL COURSE

The abrupt onset and the progressive nature of the symptoms were, at least in this group of patients, characteristic features which appear in contrast to those seen in persons with aortic insufficiency from rheumatic infections. If in addition, it is noted that our patients were usually well developed adults in the prime of life and with no previous cardiac history, the contrast is even more striking. Shortness of breath

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\* From the Medical Clinic of Western Reserve University at City Hospital

\* Read in abstract before the Association of American Physicians, Atlantic City, N J, May 6, 1924



and palpitation on exertion were the first symptoms observed by nearly every patient, and in response to the question, "When did you first notice undue shortness of breath?" they almost invariably specified a certain month or week. Prior to this time they had considered themselves well and able to work, in some instances at hard manual labor. The few who sought medical attention and were kept in bed at this stage were temporarily relieved, after getting up, however, they experienced the same incapacity for physical exertion as before.

The duration of symptoms before frank signs of heart failure appeared varied considerably. The longest period was three years in one case, the shortest two weeks, with an average of nine months. Twenty-four patients had varying grades of cardiac decompensation when first seen, and in spite of both symptomatic and antisiphilitic treatment, twenty ran a progressive downhill course to death. The four who were temporarily improved and left the hospital, were later readmitted one or more times and all died in less than a year. The longest hospital stay was seventy-eight days in one case, the shortest two days in three instances, with an average for the group of twenty-four days. Symptoms ordinarily attributed to syphilitic aortitis, i. e., substernal pain, nocturnal dyspnea, anginal attacks, etc., were noted in only one patient.

#### PHYSICAL SIGNS AND LABORATORY DATA

Only those physical findings which were more or less typical and common to the group as a whole will be considered here.

Excepting one case of tuberculous meningitis, the patients were well developed and well nourished. The excellent muscular development, particularly among some of the laborers, appeared quite consistent with their brief history of incapacity. In the white subjects, pallor of the face was the rule, but in no instance was this due to anemia, as shown by routine red blood counts and hemoglobin determination.

Most patients preferred the orthopneic position in bed. Respiratory distress closely paralleled the diminution in vital capacity from congestion at the lung bases, or more rarely, from a pleural effusion. A notable exception to this was seen in one case, J. R., who had violent dyspnea but good lung excursion, no signs of moisture at the bases, and a normal vital capacity. Cheyne-Stokes breathing was observed a few days before death in several instances. All cases, except two who were moribund when first examined, presented the characteristic vascular signs of aortic insufficiency. In approximately one-third of the patients one heard at the apex the typical presystolic Flint murmur, which in two instances was accompanied by a palpable thrill. The intensity of the thrill and the typical drum roll murmur in these two cases led two experienced observers to suspect mitral stenosis. At the

necropsy the mitral valves were normal in both cases. Without exception, every case in this series had both a systolic and a diastolic murmur frequently more intense in the third or fourth interspace along the left sternal border than in the second interspace to the right of the sternum. The harshness, intensity, and duration of the systolic murmur in some cases, and as it happened in one instance, a palpable thrill over the base of the heart, might suggest a combined aortic stenosis and insufficiency.

It is interesting to note that aortic arch dilatation was suspected in several cases but not confirmed by necropsy. Not infrequently fairly typical signs of aortic widening were elicited, which were supported by roentgenologic examination. However, after finding aortas of normal caliber at the necropsy in several cases, it became apparent that caution was necessary in making a diagnosis of aneurysm in a case of frank aortic insufficiency, even in the presence of suggestive findings. The dynamic excursion of the aorta in this condition was long ago emphasized by Osler as one of the pitfalls in the diagnosis of aortic aneurysm.

Electrocardiograms were made in several cases, and although they were seldom strictly normal, there was no one abnormality which appeared characteristic.

Fever was present in all cases with pulmonary infarction but was unusual in the others. When it did occur it was seldom above 38 C (100 F). One patient, however, without pulmonary infarction had a persistent elevation in temperature (from 38 to 38.5 C) (from 100 to 100.8 F) for several weeks before death.

The high percentage of positive blood Wassermann reactions frequently found by past writers in cases of syphilitic aortitis was also found in this series. A positive blood reaction was obtained in all but one of the twenty cases examined. In this case the test was repeated several times and was consistently negative. This high percentage (95 per cent) of positive reactions again emphasizes the significance of the test in the diagnosis of syphilis of the aorta.

#### NECROPSY FINDINGS

The necropsy material from this group of cases was interesting because of the uniformity with which certain findings appeared in every case (see the table).

#### ASSOCIATED SYPHILIS OF THE AORTA

Every patient showed syphilitic mesaortitis. In twenty, the lesion was demonstrable grossly as well as microscopically, in five, senile arteriosclerosis so obscured the gross picture that syphilitic mesaortitis could be proved only by histologic examination.

# *Clinical and Pathologic Findings in Twenty-Free Cases of Syphilitic Aortic Insufficiency*

Patient	Sex*	Race	Age	Occupation	Duration of Life after Onset of Symptoms	Heart Weight Gm	Chief Defect at Aortic Orifice	Remarks
I D	♂	Black	40	Teamster	2 yr, 2 mo	725	Sclerosed and retracted leaflets	
O B	♂	White	40	Pumpkin	3 1/2 years		Sclerosed and marked sagging of leaflets	
W S	♂	Black	39	Truck driver	2 months	500	Sclerosis and destruction of leaflets	
R B	♂	White	56	Electrician	2 months	670	Sclerosed and retracted leaflets	Right coronary artery occluded
O D	♂	White	28		5 weeks	600	Sclerosed leaflets thickened throughout	
W M	♂	Black	35	Chimney	1 1/2 years	800	Retracted sagging leaflets	
W V P	♂	Black	48	Minister	6 months	470	Retraction of leaflets	
I N	♂	White	40	Laborer	2 weeks	440	Marked retraction of leaflets	Slight encroachment on orifice of right coronary
J G	♂	Black	40	Truck driver	3 weeks	740	Sclerosis and marked sagging of leaflets	
W C	♂	Black	39	Janitor	4 months	80	Retracted, sclerosed leaflets	"Pin point" opening to right coronary
I R	♂	White	35	Toolmaker	1 year	810	Destruction of entire noncoronary and part of right coronary leaflets	
Chas. D	♂	White	42	Real estate dealer	1 year	640	Primary ring dilatation	Fusiform dilatation of aorta
I R	♂	Black	39	Rooming house proprietor	9 weeks	700	Marked sagging of leaflets	Right coronary partially occluded
V	♂	White	45	Chiropractor	16 months	1 000	Retracted leaflets greatly thickened at free margin	Marked simple arteriosclerosis of aorta
Wm M	♂	Black	39	Musicien	4 months	900	Primary ring dilatation	Secondary aneurysm of ascending aorta
M J	♂	White	37	Woodworker	7 weeks	650	Thickened and retracted leaflets	Diffuse dilatation of aorta with marked simple arteriosclerosis
I I	♂	White	62	Sailor	6 months	800	Leaflets thickened and rigid	
V W	♀	Black	44	Housewife	1 year	725	Sclerosis and slight retraction of leaflets	
S W	♂	White	39	Milk distributor	2 years	650	Sagging of leaflets	Marked simple arteriosclerosis of aorta right coronary occluded
S H	♂	Black	40	Laborer	Menigitis for 3 weeks	350	Sclerotic leaflets, rolled at free margins	Complete occlusion of right coronary partial occlusion of left coronary
G Y M	♂	White	64	Carpenter	1 year	725	Sclerotic, retracted leaflets	Right coronary completely occluded left coronary partially so
G W	♂	Black	40	Laborer	3 years (?)	550	Thickened and retracted leaflets	Marked simple arteriosclerosis of aorta with slight dilatation aneurysm involving noncoronary sinus of Valsalva
Geo W	♂	White	47	Victrol polisher	3 months	675	Thickened, sagging and retracted leaflets	
A I	♂	White	63	Teamster	2 years	600	Primary ring dilatation	
A K	♂	White	43	Printer	2 years	750	Primary ring dilatation	

\* In this column ♀ indicates female ♂ male



Fig 1—The retraction and thickening of the right and noncoronary leaflets. Note the extensive simple arteriosclerosis of the aorta involving the sinuses of Valsalva and the plaque spreading the leaflet insertions.



Fig 2—The marked thickening and retraction of the right and noncoronary leaflets. Note the rolled appearance of the free borders and the hyaline plaque at the common site of insertion.

## APPEARANCE OF THE VALVULAR AREA

In every instance the normal architecture of the valvular area was distorted so as to produce insufficiency at the orifice during diastole. Not a single case was observed in which an actual impediment might have occurred to the passage of blood from the left ventricle into the aorta. Either the ring itself was dilated or the integrity of the leaflets was lost, or, as occasionally happened, both processes were present. In any event, the picture was invariably that of aortic insufficiency and never of stenosis.

## HYPERTROPHY OF HEART

With the exception of one case (tuberculous meningitis) all patients had hypertrophied hearts manifested primarily by thickening of the left ventricle. The heaviest of these weighed 1,000 gm, the lightest 440 gm, with an average weight for the group of 642 gm. Some degree of dilatation of the left ventricle was a consistent finding, extreme in some instances, moderate in others. Occasionally the right ventricle also showed some hypertrophy and dilatation, but never to the same extent as that seen in the left. The gross picture of the heart muscle differed in no way from that seen in hypertrophied hearts from other causes, i. e., hypertension. Varying grades of connective tissue proliferation were noted, either as a diffuse fibrosis, or as patchy cicatricial areas.

## ABSENCE OF DISEASE OF OTHER HEART VALVES

No patient was diseased in the other cardiac valves. Although this may have been a coincidence it illustrates a point noted by past writers, namely, that syphilis need hardly be considered a cause of valve disease, except as it attacks the aortic area. So far as we could determine, syphilis appeared to be the sole factor in all cases, as no instance was observed in which a sclerotic syphilitic valve was the seat of another infection.

In addition to the before mentioned features, seen in all cases we may now consider some aspects of the pathologic changes appearing in individual cases. For example, there was no relation between the severity of the disease process in the aorta and the degree of involvement of the aortic leaflets. In some hearts a high grade of functional insufficiency was obvious, from distortion or actual destruction of the leaflets with only minimal lesions localized in the suprasygmoid region. In other instances the aorta was extensively diseased, occasionally it was the seat of a diffuse dilatation or a definite aneurysm (three cases in this series) while the leaflets appeared little deformed.

Various deformities of the valve leaflets occurred much more frequently than ring dilatation. Some of the more typical of these are shown in the accompanying photographs for which I am indebted to



Fig 3—The marked destruction of the aortic leaflets, the right coronary is reduced to little more than a fibrous cord while the noncoronary leaflet is completely detached except at the point shown and hangs free in the blood stream

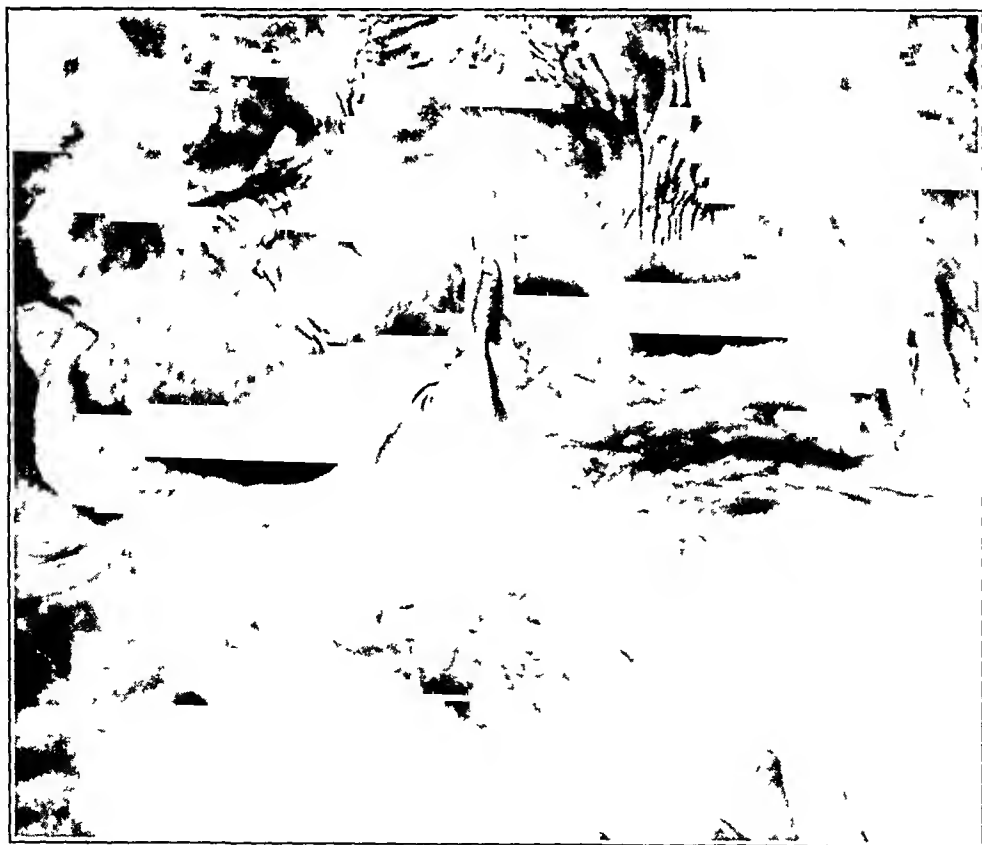


Fig 4—The characteristic sagging of the right and noncoronary leaflets. Note the hyaline plaque at the site of insertion of the two leaflets

Prof T Wingate Todd and his staff at the Anatomical Laboratory In some instances the leaflets were thick, rigid, or they were reduced in size, both in depth and in width, and appeared as mere fibrous cords (see Figs 1 and 2) In other cases only the free margin was thickened or curled into a cord-like roll The most striking example of leaflet destruction (shown in Fig 3) occurred in the case of J R, a white man, aged 35 All that remained of the right coronary leaflet was a fibrous fold along the attached border, while the noncoronary leaflet was detached throughout most of its width, and reduced in size to a mere fibrous cord which hung free in the blood stream

The simplest valve defect noted was a curious sagging of the free border of one or more cusps, as shown in Figure 4 On closer inspection this was found to be due to a hard, pearly, nodular plaque implanted at the site of the common insertion of adjacent cusps Either by gradual elevation or by extension downward, the plaque had carried with it the valve insertions, which were in some instances situated several millimeters below the normal site of attachment This resulted in a characteristic drooping of the free margin and in a few cases, particularly in the younger subjects, was the chief defect at the orifice From the study of the gross picture in several such cases, it appears that syphilis spreading from the aorta toward the heart can attack no more vulnerable spot than the site of insertion of the aortic leaflets

The syphilitic changes at the root of the aorta were in some cases most severe in and about the sinuses of Valsalva, distorting the structures and frequently involving the coronary orifices The right coronary was completely occluded in four cases and in two of these the left was also appreciably narrowed In two other instances the right vessel opening was partially blocked so that every fourth case in this series had some degree of coronary obstruction In this connection, it is interesting to note that in spite of the active disease surrounding their orifices, the coronary vessels themselves were seldom involved When opened they presented a smooth, normal intima Exceptions were of course seen in the older patients with intimal arteriosclerosis

In order to visualize the functional defect at the aortic orifice (the actual leak) more clearly than was possible by simple inspection of the opened specimen, the following procedure was employed The aorta was cut just below the mouth of the innominate and removed with the heart A slit large enough to admit two fingers was made in the cavity of the left ventricle, which was washed clean of blood and clots The heart was supported and the aorta rendered just taut enough that the aortic ring was not artificially distorted The cavity of the ventricle was illuminated through the slit by a pocket flash light, while water was run into the aorta This simple method illustrated the functional significance of the anatomic change at the aortic orifice

It was deemed advisable, particularly for teaching purposes, to procure a permanent specimen which would illustrate the defect as observed in some of the more typical cases. After obtaining a view of the aortic area by the simple water method, the cavity of the left ventricle and the aorta were carefully dried. The ventricle was filled with cotton, care being taken not to distend the cavity nor to encroach on the aortic orifice. The heart was supported and hot paraffin was poured into the aorta. Hardening was hastened by carefully lowering the organ into cold water. The aorta was now slit to within a few centimeters of the ring, the paraffin plug was withdrawn and its lower end cast in plaster. After a little practice, models were obtained which quite accurately reproduced the conditions viewed directly by the water method. A model made from a heart showing both ring dilatation and leaflet involvement is reproduced in Figure 5. Models were also made from normal hearts, which showed perfect coaptation of the three leaflets, as shown in Figure 6. In fact, a certain redundancy at the free border of the valves was noted, suggesting that normally the aortic orifice may undergo slight dilatation and yet not be incompetent. This redundancy may serve as a factor of safety under such conditions as vigorous exercise.

Histologic examinations of the aorta and heart were made in every case. In three hearts removed in less than an hour after death, a careful search was made for spirochetes, but not any were found. For the following résumé of the positive microscopic findings in twenty-three of the twenty-five cases I am indebted to Prof. Howard T. Karsner.

#### MICROSCOPIC FINDINGS

*Aorta*—Syphilitic mesaortitis was easily distinguishable in all but four cases, in which the diagnosis was nevertheless clearly established. The destruction of the media was conspicuous in twelve cases, but less marked in eleven.

*Heart*—The epicardium showed in varying degree an infiltration of lymphoid, plasma, and endothelial cells in all but six cases. The heart muscle showed in all but one case the changes in the nuclei significant of hypertrophy, i. e. increase in the lateral diameter with squared ends. Cloudy swelling, indicated by diminution or disappearance of transverse striations was found in all but two hearts.

In all instances there was some lesion of the heart muscle, either old or recent. In thirteen hearts there were minute areas in which muscle had disappeared and was replaced by connective tissue. Aside from the cloudy swelling, regarded as of little special significance, hyalinization of muscle, without disappearance of nuclei or other signs of definite fresh necrosis, was marked in two cases, moderate in one, and slight in three. Hydropic infiltration, indicated by definite vacuolization of the muscle fiber cells, was marked in three cases, slight in seven and absent in the others.

Segmentation of notable degree was found in seven instances. Only two hearts failed to show any recent change in the muscle.

The connective tissue showed overgrowth in all cases, this was most marked in the neighborhood of blood vessels except in four cases with only moderate



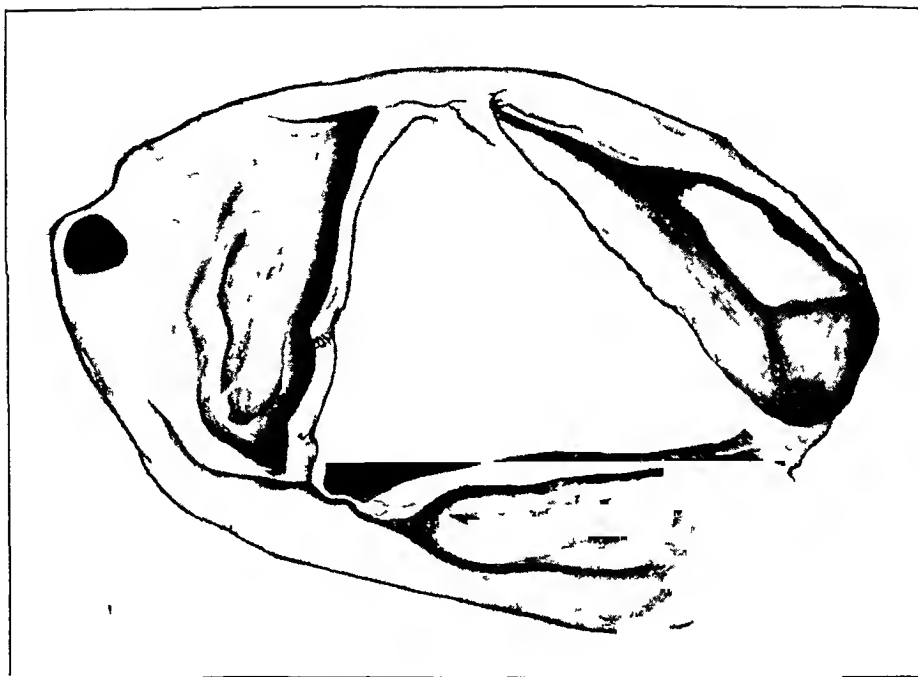


Fig 5—A model of the aortic orifice (approximately twice natural size) from a heart showing both ring dilatation and leaflet involvement. The free margins of the thickened and retracted leaflets fail to approximate, leaving the triangular shaped opening shown in the center.

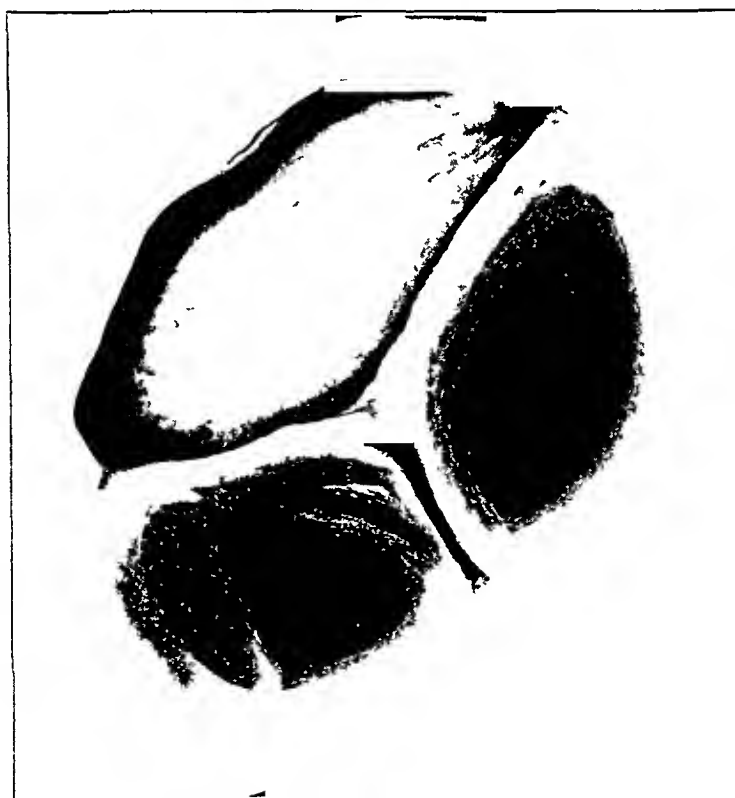


Fig 6—A model of a normal adult aortic orifice (approximately twice natural size). Note the perfect coaptation of the three leaflets.

fibrosis Infiltration of lymphoid and other mononuclear cells was observed in all but six instances Basic staining of the connective tissue and interfibrillar substance, interpreted as due to mucoid, was found in all but seven cases

The combination of fibrosis, cell infiltration and mucoid, comparable to the histologic picture of syphilitic myocarditis as described by Warthin, was found in eight instances Cicatricial types of fibrosis were found in four cases This was associated with demonstrable intimal sclerosis of the smaller arteries in one case only, where infarcts were also present

#### COMMENT

Thus far we have described the clinical and pathologic facts observed in twenty-five proved cases of syphilitic aortic insufficiency An attempt will be made to correlate these facts, and where the evidence warrants, to suggest certain deductions whose final confirmation will require a longer study of more abundant material

Mention was made of the fact that the first symptoms noted by the majority of patients were those referable to myocardial impairment, i e., shortness of breath and palpitation on exertion Although syphilitic mesaortitis was demonstrated at necropsy in every case, the symptoms ordinarily attributed to aortitis (substernal pain and oppression, anginal attacks, a vice-like constriction about the chest, etc.) were conspicuously absent No doubt some patients gave inaccurate accounts or perhaps disregarded their early symptoms but so far as could be determined the majority had no symptoms at least none which in any way interfered with their daily occupation, while the disease was confined to the aorta alone This observation is difficult to reconcile with the views of Allbutt, Wenckebach, and others, on the dependence of angina pectoris upon aortitis In discussing this subject Allbutt<sup>1</sup> writes "No cause of angina comes more clearly into view than syphilis" Whether the absence of early symptoms of aortitis may be ascribed to the nervous organization of the type of patient studied, mostly of the laboring class and approximately 50 per cent negroes, is an interesting question

The progressive heart failure seen in this group of patients was sufficiently striking compared to other types of heart disease, to merit some consideration of the factors involved in the heart's exhaustion Twenty patients failed to recover from their first cardiac breakdown One clear reason for this is the fact that they did not seek medical attention until frank signs of circulatory failure appeared A study of the necropsy findings, however, suggested that other factors may play an important part in determining the prognosis in this disease

Syphilitic involvement of the aortic area produces a functional insufficiency at the valve orifice either by dilatation of the ring or destruction and distortion of the valve leaflets, while a combination of the two

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<sup>1</sup> Allbutt Clifford Diseases of the Arteries Including Angina Pectoris, Vol 11 London, The MacMillan Co., 1915, p 422

processes is frequently seen. In any event a leak in diastole occurs, and while this is still small, perfect compensation may be established. But from the very nature of the pathologic changes, the functional lesion tends to be a progressive one, and, developing rapidly, it throws an insuperable burden on the heart which cannot keep pace in establishing compensation.

We have found from inspection by the water method, and from casts made in several cases, that as much as one-half or even more of the total area of the aortic orifice may be rendered insufficient by syphilis, and important from the functional standpoint is the fact that the actual leak occurs in the very center of the stream. Under these circumstances it seems probable that a considerable quantity of blood must actually regurgitate into the ventricle during diastole. Another important factor bearing on the heart's capacity to compensate is the interference with the coronary circulation. One out of four cases in this series had some degree of coronary occlusion.

Narrowing of the coronary openings apparently takes place gradually in syphilis, thereby affording time for the development of collateral circulation between the right and left vessels, otherwise it would be difficult to explain the hypertrophy attained by some hearts showing complete occlusion of the right coronary artery with appreciable narrowing of the left (two instances in this series). Oberhelman and LeCount<sup>2</sup> have recently emphasized this point. They believe, from their roentgen-ray studies of the coronary circulation in normal and pathologic hearts, that the extent of the anastomosis between the two vessels is not a matter of age as taught by Gross<sup>3</sup> and others, but is determined in part by the rapidity with which the occluding process develops. Important as this compensatory anastomosis may be, it must ultimately fail in the face of the progressive coronary narrowing which occurs in syphilis.

So far as function may be influenced by anatomic change, it is clear that syphilis at the aortic area is a particularly grave lesion, destroying the integrity of the leaflets on the one hand, and impairing the blood supply to the heart on the other. Singly or in combination these impediments must seriously handicap the heart, and disposed by their nature to progress, they appear to be the most important factors determining prognosis in syphilitic aortic insufficiency.

It was not possible to determine the functional significance of the myocardial changes found in these cases. In eight instances the picture

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2 Oberhelman, H. A., and LeCount, E. R. Variations in Anastomosis of the Coronary Arteries and Their Sequences, *J. A. M. A.* **82** 1321 (April 26) 1924.

3 Gross, Louis. The Blood Supply to the Heart in its Anatomic and Clinical Aspects, New York, Paul B. Hoeber, 1921.

was that which Warthin<sup>4</sup> attributes to latent syphilis, in fifteen others the changes in the muscle were indistinguishable from those frequently found in hypertrophied hearts from other causes. Certainly in the majority of cases the amount of apparent histologic damage seemed quite insufficient to explain the progressive myocardial failure observed clinically.

#### SUMMARY

A series of twenty-five patients with syphilitic aortic insufficiency was observed clinically, and the diagnosis confirmed by postmortem examination in every instance. The anatomic changes found in all cases were (1) syphilitic mesaortitis with extension of the process to the aortic area causing insufficiency at the orifice, and (2) hypertrophy and some degree of dilatation of the heart, chiefly of the left ventricle. One case in four had some grade of coronary occlusion. It was suggested that the progressive widening of the aortic orifice, either from leaflet involvement or ring dilatation, and occlusion of the coronary arteries are the chief factors responsible for the relatively short duration and uninterrupted progression of the heart failure observed in these patients. The histologic changes in the heart muscle were similar to those frequently seen in hypertrophied hearts from other causes. To attribute these changes to latent myocardial syphilis seems unwarranted by the evidence afforded by this series of cases.

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<sup>4</sup> Warthin, A. S. *The New Pathology of Syphilis*, Harvey Lectures, 1917-1919, p. 67-96.

# RELATIONS BETWEEN GASTRIC ACHYLIA AND SIMPLE AND PERNICIOUS ANEMIA \*

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## INTRODUCTION

Fenwick<sup>1</sup> was the first to demonstrate the occurrence of gastric achylia in pernicious anemia, he thought that this might be the cause of the anemia, but emphasized the atrophy of the gastric mucosa. The discussion which followed, therefore, dealt mainly with this atrophy, and when it was found that achylia might be present without atrophy Fenwick's hypothesis lost ground and both anemia and achylia were generally considered coordinated phenomena due to some toxic influence. At the International Congress of Medicine in London (1913) one of us (K F) again put forward the hypothesis that the anemia frequently found with achylia gastrica was a secondary phenomenon produced by the lack of gastric secretion even though no atrophy could be demonstrated. In support of this theory he described three cases of pernicious anemia, in which achylia and normal hemoglobin had been found from three to nine years before the onset of the symptoms of anemia. He also stated that not only pernicious anemia, but also a simple anemia of chlorotic type might occur associated with gastric achylia. Later different authors have described cases of pernicious anemia in which achylia was found long before the beginning of the anemia (Kuttner, Cobet and Morawitz, Levine and Ladd, Bie, Hunter<sup>2</sup>). The theory has recently been supported by Hurst<sup>3</sup>.

## FREQUENCY OF GASTRIC ACHYLIA IN PERNICIOUS ANEMIA

In a former paper Faber and Bloch<sup>4</sup> presented a series of thirty cases of pernicious anemia, all except one showing achylia.

According to Finnish observers a gastric achylia is frequent in bothrioccephalus anemia, but not nearly so frequent as in idiopathic pernicious anemia, for more than 25 per cent of the cases of anemia due to tapeworm showed a normal acidity of the gastric contents.

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\* From the medical clinic of the University of Copenhagen

1 Fenwick, S. *Lancet* 2 78, 1870, 2 1, 39, 77, 1877

2 Kuttner, L. *Spez Path u Therap* 5 679, 1914. Cobet, R, and Morawitz, P. *Ztschr f ang Anat* 6 244. Levine, S A, and Ladd, W S. *Bull Johns Hopkins Hosp* 32 254 (Aug.) 1921. Bie, V. *Lancet* 1 631, 1922. Hunter Charles. *Canad M A J* 13 38 (Jan) 1923.

3 Hurst, S A. *Lancet* 1 111 (Jan) 1923

4 Faber, K, and Bloch, C E. *Ztschr f klin Med* 40 98, 1900

Throughout a long period of observation we have seen only four cases of pernicious anemia with normal gastric secretion. The total number of patients with pernicious anemia treated in the clinic between 1907 and 1922 was fifty-four. Achylia was demonstrated in forty-seven cases, three for various reasons were not subjected to a test meal, while four, as before mentioned, showed the presence of free hydrochloric acid. Disregarding the patients not examined we found achylia in 92 per cent of our cases.

The symptoms and blood picture in these four patients, the histories of which are given at the end of the paper, are so characteristic that they cannot be distinguished from ordinary pernicious anemia.

This, of course, does not settle the question whether achylia, when found, is of pathogenic importance for the anemia, it only means that there must be other possible causes. As already pointed out pernicious anemia can occur without achylia in patients harboring the bothriocephalus tapeworm, it is true that in the pernicious anemia of pregnancy, where the blood picture may be quite similar to that of idiopathic pernicious anemia, achylia may be absent. Levine and Ladd conclude from their series that it is doubtful whether cases without achylia should be classified as pernicious anemia, and that such anemias ought to be considered as probably due to some definite cause. One must inquire whether any etiology could be demonstrated in our four cases. In the literature are reported cases of pernicious anemia in syphilis. Our first patient had an untreated syphilitic infection, but the anemia did not respond favorably to antisiphilitic treatment. In the other three cases there were absolutely no etiologic factors to be found, not even the possibility of a syphilitic infection as the cause. We must then admit that the cause in these cases is entirely obscure, and we may pass to a consideration of the relation between pernicious anemia and achylia when the latter is present.

#### ACHYLIA PRECEDING PERNICIOUS ANEMIA

It is generally recognized that many patients with pernicious anemia have suffered from gastro-intestinal symptoms for years before the onset of anemia, but this is no proof that achylia precedes anemia unless an examination has shown at some time achylia associated with normal blood findings. This, or at least normal hemoglobin, has been demonstrated in four patients whose histories are given at the end of the paper.

The diagnosis of pernicious anemia in these patients was well supported and was confirmed by necropsy in two of the cases. The achylia was demonstrated from three to twelve years prior to the onset of the anemia, and a normal hemoglobin percentage was found in the early determinations. Levine and Ladd published in 1921 three cases in which

achylia was found long before clinical anemia supervened. These observations show at least that the achylia cannot be attributed to the anemia, although it may be a factor leading to anemia.

In connection with the latter hypothesis it is interesting to note the observations of Hartman,<sup>5</sup> who saw pernicious anemia develop two or three years after complete gastrectomy. This would tend to show that the anemia cannot be due to the diseased stomach, but that the cause is to be sought in the intestines, the contents of which are altered by the lack of gastric digestion whether this be brought about by achylia or by complete gastrectomy.

A further support of this explanation is found in instances of pernicious anemia arising in association with chronic intestinal obstruction, which were first reported by Faber<sup>6</sup> (1895), later Meulengracht<sup>7</sup> was able to collect data on eight such cases.

In oriental sprue, Dutch observers have frequently found an anemia which could not be distinguished from idiopathic pernicious anemia, this also may be due to disturbed intestinal digestion.

#### ACHYLIA GASTRICA AND SIMPLE ANEMIA

In a paper by Faber<sup>8</sup> (1923) there was given a statistical review of 207 cases of achylia in which the blood had been examined. Twenty-two of these patients suffered from genuine pernicious anemia. Thirty-seven of the remaining 185 patients had hemoglobin below 65 per cent and fifteen of the thirty-seven below 50 per cent. These anemias were of the simple chloro-anemic type. A simple anemia, even when the rather low after limit of 65 per cent hemoglobin is used, is a not infrequent finding in association with achylia. This anemia is of a rather benign character and transition to pernicious anemia has not been observed. While the anemia is not lethal, it is somewhat refractory toward treatment and tends to recur. The most successful treatment in these cases appears to be large doses of iron (from 0.5 to 1 gm. of reduced iron U. S. P. three times a day). The anemias occur in both sexes and at all ages and have not a tendency to spontaneous or permanent recovery.

In order to investigate the frequency of this complication we have for a period of several years subjected all our achylia cases to a careful blood examination. Patients with cancer, tuberculosis and pernicious anemia were excluded. As achylia we include the patients who at repeated examinations with Ewald's test meal showed no reaction to Boas' reagent and Congo red and poor chymification of the gastric con-

5 Hartman, H. R. *Am J M Sc* **162** 201 (Aug.) 1921

6 Faber, K. *Berl klin Wchnschr* **34** 643, 1897

7 Meulengracht, E. *Acta Med Scand* **56** 432 (April) 1922

8 Faber, K. *Berl klin Wchnschr* **1** 958, 1913

tents The blood was examined for hemoglobin, red blood cells and white blood cells and the index was calculated. Stained dry films were carefully examined for the changes found in pernicious anemia. Differential counts were not made in all cases, but frequently a relative lymphocytosis was noted. Neither the leukocyte count nor the dry film findings are noted in the tables given at the end of the paper, since the changes found were generally slight (anisomicrocytosis) and never suggestive of pernicious anemia. Before proceeding further we shall give the normal figures with which these results are to be compared.

In agreement with Bie and Møller's<sup>9</sup> earlier findings in this clinic, Gram and Norgaard<sup>10</sup> found the normal values for hemoglobin, red blood cells and color index given in Table 1.

As a result of quadruplicate counts and standardized technic the ordinary, not inconsiderable, error in the cell count was reduced, so that the index varied very much less than under ordinary clinical con-

TABLE 1—*Normal Values for Hemoglobin, Red Blood Cells and Color Index*

	Men			Women		
	Hemo- globin per Cent	Red Blood Cells, Millions per C Mm	Index	Hemo- globin, per Cent	Red Blood Cells, Millions per C Mm	Index
Maximum	118	5.91	1.02	102	5.05	1.04
Minimum	96	4.85	0.99	88	4.36	0.97
Average	105	5.45	1.00	94	4.65	1.01

ditions. The mean error in the hemoglobin determinations (with ten readings of each dilution, in the Autenrieth colorimeter) even under ordinary clinical conditions is in our experience only from 0.9 to 1.1 per cent hemoglobin, and in these observations all of the determinations were made by the same observer.

We have considered men whose hemoglobin was less than 96 per cent and women with less than 88 per cent as anemic. It is, therefore, necessary to consider the men and women separately. Our material, the findings on which are detailed at the end of the paper, consists of ninety cases which we divide into the following groupings: uncomplicated achylia (sixty-three cases), achylia in exophthalmic goiter (fourteen cases) and achylia in chronic polyarthritis (thirteen cases).

1. Uncomplicated achylia (twenty-one men and forty-two women). This first and most important group consists of patients admitted to the wards for various gastro-intestinal troubles and in which complete achylia was found. A careful examination and the later history excluded cancer.

<sup>9</sup> Bie, V., and Møller, P. *Arch d mal du cœur* **15** 177 (April) 1922.

<sup>10</sup> Gram, H. C., and Norgaard, A. *Relation Between Hemoglobin, Cell Count and Cell Volume in the Venous Blood of Normal Human Subjects*, *Arch Int Med* **31** 164 (Feb.) 1923.



A very considerable proportion of these patients (36.5 per cent) were anemic, many of them markedly so.

In cases with normal hemoglobin the color index fluctuated around 1 while the index in the anemic cases nearly always was decreased. In the more pronounced cases the microcytosis was clearly visible in the stained films.

2. *Achylia* in exophthalmic goiter (one man and thirteen women). In exophthalmic goiter *achylia* is so generally encountered that we do not possess a control material allowing us to say whether this disease, *per se*, causes an anemia.

Anemia was found in 36 per cent of these cases, but it was never very severe. In this group also the index tends to be lower in the anemic cases than in those with a normal hemoglobin percentage.

3. *Achylia* in chronic deforming polyarthritis (two men and eleven women). *Achylia* is a very frequent finding in this disease, but only our cases with *achylia* have been studied hematologically.

In this group anemia was even more intense and frequent, being found in 69 per cent of the cases. We also observed the same tendency to low index in the anemic cases. The greater frequency of anemia in this disease may be due to other factors tending to produce anemia.

Considering all three groups as one we find among ninety cases of *achylia* thirty-seven (or 41 per cent) which showed hemoglobin below the lowest normal values established in our clinic. This anemia is often slight but may reach values as low as 45 per cent of hemoglobin in men (index, 0.6) and 34 per cent in women (index, 0.5).

The anemia was distinctly more frequent in women than in men, and most of the severe cases occurred among the former. As to the character of the anemia, it was nearly always pronouncedly microcytotic with a low color index. A marked increase of the index was never observed, the cases showing a slight elevation of index above 1 showed normal figures on repeated careful examination.

While the cases with normal hemoglobin showed absolutely normal red cells in the dry films, the preparations from anemic patients often showed a decided anisomicrocytosis. Evidence of forced regeneration (polychromatophil, reticulated or nucleated reds) was found only during treatment with large doses of iron, never in the untreated cases.

Megalocytes or megaloblasts were never observed, in spite of careful search with the ocular micrometer.

Concerning the leukocytes it need only be mentioned that the absolute number was normal or slightly low. Differential counts were not performed on all cases, but frequently showed a relative lymphocytosis, especially in the cases of exophthalmic goiter.

Observations on four cases of pernicious anemia showing normal gastric secretions are presented.

## REPORT OF CASES

CASE 1—A W, a woman, aged 25, unmarried, was admitted to hospital Oct 28, 1919 Her family history was negative except that a sister was said to have had anemia for a time There were no previous significant diseases except for grip in November, 1918, since then the patient had been pale and tired In the three months before admission there was increasing pallor and shortness of breath

*Physical Examination*—Extreme waxy paleness was noticed, although the patient was well nourished There were several small hemorrhages in the retina There were no clinical signs of syphilis Wassermann reaction was strongly positive at three successive determinations

Ewald test meal (one hour) was given October 27 to the amount of 106 c c Boas reagent revealed traces of free hydrochloric acid The free acidity with Congo red paper, 31 The total acidity with phenolphthalein, 56 There was no slime Chymification was good November 11, an Ewald test meal was given Boas reagent 20 \* Free acidity with Congo red, 35 \* Total acidity with phenolphthalein, 50 \* There was no slime and chymification was good

There was no blood or parasite eggs in the feces In the middle of November a sore throat developed, at which time a small ulcer was found on the right tonsil Smears from this showed fusiform bacteria but no spirochetes

TABLE 2—*Blood Examination*

Date	Hemo- globin, per Cent	Red Blood Cells Millions per C Mm	Index	Leuko- cytes, per C Mm	Plasma Color (Meulen- graecht)	Platelet Count per C Mm	Stained Film
10/28	29	1.05	1.4	2 700	3	22,000	Anisopoikilomegalocyto- sis, no nucleated red
11/ 1	28	0.96	1.5	1 800	2	25,000	A few basophil reds
11/ 8	31	1.07	1.5	1 500	3	41,000	A few basophil and nucle- ated reds
11/15	36	1.18	1.5	1 800	3		Several nucleated, among which one typical mega- loblast
11/21	31	1.27	1.2	2 700	3	23,000	
11/28	38	1.86	1.4	2 500	2	41,000	
12/ 7	33	1.31	1.3	3 800	4	26,000	
12/17	26	0.98	1.3	2 800			
12/19	20	0.80	1.25	1 300			

There was a very pronounced hemorrhagic diathesis, as a result of which transfusion was only a partial success There was slight fever now and then The patient was treated with arsenic in various forms, mercury and potassium iodid

There was steady deterioration, and the patient died December 24 Necropsy was refused

Micrometry of the red cells showed (November 8) an average diameter of 89 microns Differential count (November 21) neutrophils, 48 per cent, eosinophils, 3 per cent, lymphocytes, 40 per cent, monocytes, 7 per cent, basophils, 2 per cent There were no abnormal types of leukocytes The results of the blood examination are seen in Table 2

CASE 2—E P, a man, aged 64, married, was admitted June 12, 1920 He had been constipated for many years, and had frequent catarrhal infections of nose and throat Three months before admission the patient had a sudden attack of vomiting and diarrhea Since then he had been ill, with increasing pallor and weakness

*Physical Examination*—Extreme anemia without perceptible jaundice Apart from a slight emphysema of the lungs there were no marked changes in the organs The patient had slight fever now and then

\* C c one-tenth normal NaOH per 100 c c test meal changes the reaction

Ewald test meal (1 hour) June 14 and 18 The free acidity with Congo red was 19 and 53 The total acidity with phenolphthalein, 50 and 83 There was no slime The chymification was good each day

In spite of treatment the patient became more and more anemic and died August 3 Necropsy disclosed anemia, myocardial degeneration, hypertrophic gastritis and hypostatic pneumonia

TABLE 3—*Blood Examination*

Date	Hemo globin, per Cent	Red Blood Cells Millions per C Mm	Index	Leuko cytes, per C Mm	Plasma Color (Meulen graecht)	Platelet Count per C Mm	Blood Films
6/14	42	1.34	1.6	7 000	5	447,000	Anisomegalocytosis, no nucleated rids
6/21	36	1.04	1.7	9 900	3	453 000	
6/28	28	0.95	1.5	7 500	3	265,000	
7/ 5	22	0.84	1.3	6 700			
7/12	17	0.64	1.3	4 200			
7/19	16	0.63	1.2	2 500			
7/26	26	0.92	1.4	2 400			

The differential leukocyte count was normal

CASE 3—T P, a woman, aged 26, unmarried, was admitted Oct 29, 1920 Her past and family history were negative Six months before admission there was increasing lassitude, later vertigo and functional dyspnea

*Physical Examination*—The patient was pale with a subicteric tint The organs were normal except for systolic murmurs over all of the heart valve areas

Ewald test meal (1 hour) October 21 The free acidity with Congo red, 22 The total acidity with phenolphthalein, 62 There was no slime, and chymification was good

There was no improvement in spite of treatment with arsenic, iron and transfusion There was slight fever with a few sudden rises in temperature The patient died Dec 16 Necropsy disclosed anemia, hyperplasia of the bone marrow, fatty degeneration of myocardium and liver, pulmonary infarction and bilateral pleurisy

TABLE 4—*Blood Examination*

Date	Hemo globin per Cent	Red Blood Cells Millions per C Mm	Index	Leuko cytes, per C Mm	Plasma Color (Meulen graecht)	Platelet Count per C Mm	Blood Films
10/21	30	1.14	1.3	9 100	6	45,000	Pronounced anisomegalocytosis, no nucleated rids
10/24	31	1.16	1.35	8 500	6	56,000	As previous, several megaloblasts and monoblasts
10/27	29	0.99	1.45	4 200	6	34 000	A few megaloblasts
11/ 2	28	0.91	1.6	8 500			
11/ 9	25	0.82	1.6	6 200			
11/21	26	0.71	1.9	5 900			

Average diameter of red corpuseles 82 microns (October 27) Differential counts (limits in 5 counts) neutrophil, from 83 to 61, eosinophil, from 2 to 0, basophil, from 1 to 0, monocytes, from 6 to 2, lymphocytes, from 34 to 13

CASE 4—E J, a woman, aged 30, unmarried, was admitted Aug 31, 1920 The patient had always suffered from "chlorosis" Recently the symptoms were aggravated with weakness, vertigo and dyspnea

*Physical Examination*—The patient was very pale with a slight subicteric tint The heart was located at the left sternal margin of the fourth rib and

2 inches outside the mammillary line The second pulmonary sound was accentuated There were strong systolic murmurs increasing in intensity toward the base of the heart The spleen was slightly enlarged

	Ewald Test Meal (1 Hour)				
	Amount, Cc	Congo red, N/10 Solution of Sodium Hydroxid, Cc to 100 Cc Gastric Contents	Phenolphthalein N/10 Solution of Sodium Hydroxid, Cc to 100 Cc Gastric Contents	Slime	Chymifi- cation
September 2	223	10	40	0	Good
September 9	127	40	60	0	Good
October 5	86	38	60	0	Good
December 16	115	26	48	0	Good

Treatment with arsenic led to rapid improvement to a certain point and the patient was discharged April 12, 1921, somewhat improved The temperature was normal The heart changes were not affected by treatment

TABLE 5—Blood Examination

Date	Hemo- globin, per Cent	Red Blood Cells Millions per C Mm	Index	Leuko- cytes, per C Mm	Plasma Color (Meulen- gracht)	Platelet Count per C Mm	Blood Films
9/12	59	2.04	1.4	3,700	7	160,000	Slight anisomegalocytosis, no nucleated reds, sev- eral polychromatophil reds
9/18	82	3.66	1.1	3,400	3	201,000	
9/24	78	3.44	1.1	4,300		204,000	
10/ 5	82	3.50	1.2	2,700	2	167,000	
10/18	71	2.88	1.2	2,800	3		
11/ 3	78	3.05	1.3	4,600			
3/14/21	88	3.65	1.2	5,200			A few nucleated reds, all of the normoblast type

The average diameter of the red corpuscles (November 13) 8.5 microns Differential count (limits in 4 counts) neutrophil, from 79 to 56 per cent, eosinophil, from 3 to 1 per cent, monocytes, from 6 to 2 per cent, basophils, none, lymphocytes, from 35 to 16 per cent

#### FOUR CASES IN WHICH ACHYLIA AND NORMAL HEMOGLOBIN WERE FOUND BEFORE THE ONSET OF PERNICIOUS ANEMIA

CASE 1—P. L., a man, aged 31, was first examined in 1903. He had a history of cardialgia, irregular bowel movements and painful, red tongue (Hunter's glossitis) for eighteen months. He was not pale. In 1907 the hemoglobin (Sahli) was from 85 to 90 per cent (equals from 105 to 110 per cent by the Haldane test). Achylia. Congo red, none, phenolphthalein, from 12 to 20 cc\* (several test meals). In 1908, several test meals also showed achylia with no reaction to Congo red and phenolphthalein, 6\*. In 1910, there was increasing pallor and weakness. The patient was admitted to the clinic in 1911, suffering from extreme anemia, slight jaundice and small retinal hemorrhages. A test meal showed achylia. Congo red, none, phenolphthalein, 27 cc\*. There was no blood in the feces. The patient died May 2, 1911. Necropsy showed universal anemia, fatty degeneration of the organs and megaloblastic degeneration of the bone marrow.

\* A cubic centimeter of tenth normal sodium hydroxid per hundred cubic centimeters gastric content changes the reaction.

TABLE 6—*Blood Examination*

Date	Hemoglobin, per Cent	Red Blood Cells, Millions per C Mm	Color Index
March	28	0.85	1.6
April	22	0.84	1.3
	18	0.85	1.1

CASE 2—C K, a man, aged 52, was first examined in 1909 because of cardialgia, anorexia and vomiting. There was no blood in the feces. Test meal Congo red, none, phenolphthalein, 31, hemoglobin, from 90 to 100 per cent (equal to from 110 to 120 per cent Haldane method). In 1910, the hemoglobin was 90 (equal to 110 per cent Haldane) and in 1911 hemoglobin 90 (equal to 110 per cent Haldane). In 1912, there was rapid development of anemia symptoms. Complete achylia by test meal (Congo red, none, phenolphthalein, 30).

TABLE 7—*Blood Examination*

Date	Hemoglobin, per Cent	Red Blood Cells, Millions per C Mm	Color Index
February	37	1.36	1.4
March	42	1.35	1.6
	40	1.39	1.4
	31	1.06	1.5
April	23	0.40	2.9 ♀

Leucopenia and several megalocytes of 10-12 microns diameter. The patient died April 17, 1912. Necropsy was refused.

CASE 3—C W, a man, aged 44, was first examined in 1902 on account of "heaviness" and oppression in the epigastrium. Complete achylia (figures lost) hemoglobin 95 (Sahli<sup>2</sup>). In 1910, the anemia began. Hemoglobin ranged between 70 and 54. Achylia (Congo red, none, phenolphthalein, 10). In 1911, the patient was admitted to the clinic. He was pale, with occasional slight jaundice. The spleen was slightly swollen. There was diarrhea, but no blood in the feces. Complete achylia. Congo red, none, phenolphthalein, 24.

TABLE 8—*Blood Examination*

Date	Hemoglobin, per Cent	Red Blood Cells, Millions per C Mm	Index
September	46	1.78	1.3
December	40	1.30	1.5

Megalocytosis, nucleated reds and leucopenia. The patient was discharged without improvement and died at home, February, 1912.

CASE 4—J P, a man, at the age of 49 had rheumatic fever, immediately thereafter a chronic diarrhea developed, which persisted for the remainder of the patient's life. The patient was examined in 1907. Hemoglobin, 100 per cent. The test meal showed complete achylia. Congo red, none, phenolphthalein, 12, pepsin, none.

In 1920, he was operated on for appendicitis. Following this he said he felt tired and dyspneic. The patient was treated for anemia with good results. In December, 1921, his condition became worse and he was admitted to the clinic. The test meal showed achylia. Congo red, none, phenolphthalein, 20, pepsin, none.

\*A cubic centimeter of tenth normal sodium hydroxide per hundred cubic centimeters gastric content changes the reaction.

TABLE 9—*Blood Examination*

Date	Hemo- globin, per Cent	Red Blood Cells, Millions per C Mm	Index	Leukocytes per C Mm	Plasma Color (Meulengraecht)	Platelet Count per C Mm
12/30/21	73	2 00	1 3	5 700	5	223,000
1/ 9/22	69	2 12	1 6	2 900	4	192 000
2/12/22	43	1 13	1 9	2 000		

Blood films showed anisopoikilomegalocytosis, but not nucleated reds. The patient died in the clinic from a complicating bronchopneumonia. Necropsy showed the typical changes of pernicious anemia with fatty degeneration of the organs.

## RESULTS OF BLOOD EXAMINATIONS IN NINETY CASES OF ACHYLIA

TABLE 10—*Uncomplicated Achyia in Twenty-One Men*

Normal Blood (16 Cases, or 76 per Cent)			Anemia (5 Cases, or 24 per Cent)		
Hemoglobin, per Cent	Red Blood Cells, Millions per C Mm	Index	Hemoglobin, per Cent	Red Blood Cells, Millions per C Mm	Index
121	5 57	1 1	96	5 24	0 9
119	5 71	1 0	91	5 15	0 9
112	5 79	1 0	69	4 16	0 8
110	5 84	0 9	67	3 72	0 9
109	5 65	1 0	64	5 13	0 6
108	5 38	1 0			
108	5 79	0 9			
106	5 24	1 0			
105	4 99	1 05			
105	5 41	1 0			
105	5 49	1 0			
104	5 43	1 0			
103	5 23	1 0			
102	5 10	1 0			
101	4 95	1 0			
98	4 99	1 0			
Max	121	5 84	96	5 24	0 9
Min	98	4 95	64	3 72	0 6
Aver	107	5 11	77	4 63	0 8

TABLE 11—*Uncomplicated Achyia in Forty-Two Women*

Normal Blood (24 Cases, or 57 per Cent)			Anemia (18 Cases, or 43 per Cent)		
Hemoglobin, per Cent	Red Blood Cells, Millions per C Mm	Index	Hemoglobin, per Cent	Red Blood Cells, Millions per C Mm	Index
123	6 07	1 0	87	5 12	0 85
107	5 66	0 9	86	5 10	0 8
105	5 16	1 0	86	4 32	1 0
105	4 59	1 1	84	4 02	0 9
104	4 80	1 1	83	4 01	1 0
104	4 82	1 1	82	4 67	0 9
103	5 16	1 0	80	5 38	0 7
102	5 23	1 0	75	4 57	0 8
101	4 66	1 1	74	3 52	1 0
101	5 66	0 9	70	4 25	0 8
100	4 93	1 0	69	4 20	0 8
98	4 92	1 0	68	4 98	0 7
98	5 06	1 0	65	4 72	0 7
97	6 44	0 75	61	5 41	0 6
97	5 23	0 9	55	3 95	0 7
96	5 10	0 9	52	3 52	0 7
96	4 50	1 1	44	2 93	0 7
94	4 65	1 0	34	3 64	0 5
93	5 00	0 9			
92	4 49	1 0			
91	4 97	0 9			
91	4 67	1 0			
90	4 75	0 95			
89	5 45	0 8			
Max	123	6 44	87	5 41	1 0
Min	89	4 49	34	2 93	0 5
Aver	99	5 08	70	4 42	0 8

TABLE 12—*Achyia in Chronic Deforming Polyarthrits in Two Men and Eleven Women*

Men						
Normal Blood (1 Case, or 50 per Cent)			Anemia (1 Case, or 50 per Cent)			
Hemoglobin, per Cent	Red Blood Cells, Millions per C Mm	Index	Hemoglobin, per Cent	Red Blood Cells, Millions per C Mm	Index	
119	6 11	1 0	92	5 27	0 9	
Women						
Normal Blood (3 Cases or 27 per Cent)			Anemia (8 Cases or 73 per Cent)			
98	4 93	1 0	84	4 98	0 8	
92	4 64	1 0	83	5 34	0 8	
92	4 37	1 1	81	4 62	0 9	
			80	4 41	0 9	
			78	4 73	0 8	
			75	4 99	0 75	
			49	4 41	0 6	
			44	4 26	0 5	
Max	98	4 93	84	5 34	0 9	
Min	92	4 37	44	4 26	0 5	
Aver	94	4 65	71	4 72	0 8	

TABLE 13—*Achyia in Exophthalmic Goiter in One Man and Thirteen Women*

Men (Anemia)						
			Anemia			
Hemoglobin, per Cent	Red Blood Cells, Millions per C Mm	Index	Hemoglobin, per Cent	Red Blood Cells, Millions per C Mm	Index	
			87	4 93	0 9	
Women						
Normal Blood (9 Cases, or 69 per Cent)			Anemia (4 Cases, or 31 per Cent)			
109	5 61	1 0	77	4 09	0 9	
106	5 88	0 9	76	4 57	0 8	
104	6 06	0 9	75	4 10	0 9	
101	4 97	1 0	75	4 61	0 8	
100	5 52	0 9				
91	5 27	0 9				
91	4 91	0 3				
91	4 71	1 0				
89	4 37	1 0				
Max	109	6 06	77	4 61	0 9	
Min	89	4 37	75	4 09	0 8	
Aver	98	5 26	76	4 34	0 9	

## SUMMARY

1 Gastric achyia is usually found in pernicious anemia. It is sometimes missing and four such cases are described.

2 In four cases, the histories and examination of which are given, gastric achyia and normal hemoglobin were demonstrated as long as twelve years before the onset of pernicious anemia.

3 The results of hematologic examination in ninety cases of gastric achyia are described. It is shown that hemoglobin below normal is present in 41 per cent of these cases or in 36.5 per cent of the sixty-three uncomplicated achyia cases. This anemia is of the type of simple anemia and may resemble a chlorosis. It differs from chlorosis by its presence in both sexes and all ages and by its tendency to recur.

# A CONSIDERATION OF THE CARDIAC ARRHYTHMIAS ON THE BASIS OF LOCAL CIRCULATORY CHANGES \*

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In a recent publication <sup>1</sup> two of us reported the results of two series of experiments on the isolated perfused heart. Based on these studies we have developed the conception that in the development and propagation of the excitatory process in the heart, the  $p_H$  of the fluid bathing its tissues is a controlling factor. It is considered that the process of excitation is intimately concerned with changes in the state of equilibrium across the cell membrane. In harmony with the hypothesis advanced by Hermann,<sup>2</sup> Brunings,<sup>3</sup> and Bernstein,<sup>4</sup> and more recently elaborated by Lillie,<sup>5</sup> it is suggested that these changes have to do with alterations in the state of polarization existing at the cell tissue fluid interface. The propagation of the excitatory process by means of adjacent tissue by the action current developed at each excited point constitutes "conduction."

It is the purpose of this paper to indicate the possible application of our conception to the arrhythmias. It is conceivable that normal and abnormal rhythms alike are expressions of the inherent "automaticity" and "conductivity" of different portions of the heart, that the same fundamental explanation should apply to the genesis of both groups. For the purpose of this discussion it is considered expedient to regard all irregularities of cardiac rhythm as due to

- 1 Abnormalities of the development of the excitatory process
- 2 Interference with its normal propagation, or,
- 3 A combination of both of these

The experimental evidence for the control of these processes by variations in the hydrogen-ion concentration of the perfusate will be summarized briefly first. We studied the isolated heart of terrapin and dogs by perfusion methods reported elsewhere. Every precaution was observed to assure accurate composition of the perfusate, to maintain

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\* From the Cardiographic Laboratory of the Johns Hopkins Hospital and University

1 Andrus, E C, and Carter, E P. Heart **11** 97, 1924

2 Hermann. Handbuch der Physiol **2** 194, 1879

3 Brunings. Arch f d ges Physiol. **100** 367, 1903

4 Bernstein. Biochem Ztschr **50** 393, 1913

5 Lillie, R S. Physiol Rev **2** 1 (Jan) 1922



a constant temperature and to supply adequate quantities of oxygen with the perfusing solution. Galvanometric records were taken by direct leads and the R-R and P-R intervals carefully measured. It was found possible to control the rate of the isolated perfused heart, both cold blood and mammalian, by changing only the reaction of the perfusing fluid from  $p_H$  7.0 to  $p_H$  7.8. The limits of the variation of

TABLE 1—*Terrapin, May 5, 1921. Control of Q-R-S Interval by Variations in the  $p_H$  of the Perfusate*

Time	$p_H$	Record	R-R	P R Seconds	Q R S Seconds
2 45	7.4	1	1.64	0.60	0.20
2 46	7.8				
2 51		2	1.68	0.54	0.16
2 58		3	1.56	0.50	0.16
3 05		4	1.60	0.70	0.16
3 12	7.1				
3 17		5	1.82	1.00	0.30
3 27		6	1.60	0.96	0.28
3 28	7.4				
3 33		7	1.66	0.80	0.24

the  $p_H$  were thus relatively narrow. The more alkaline the perfusate, the more rapid was the rate, and the less alkaline the perfusate, the slower the rate.

The experimental results are illustrated in the tables and figures. Table 1 summarizes an experiment on a terrapin's heart involving change in the  $p_H$  of the perfusate. Figure 1 illustrates the characteristic electrocardiographic record of a dog's heart, showing the effect of

TABLE 2—*Dog, June 1, 1923. Control Rate of Nodal Rhythm by Changes in the  $p_H$  of the Perfusate*

Time	$p_H$	Record	R-R Seconds	Rate	P R Seconds
2 45	7.4	1	0.80	75	0.11
2 47		Auricles cut away			
2 52		2	2.00	30	
2 53	7.8				
2 55		4	0.78	77	
2 58	7.4				
3 03		6	2.20	27	
3 05	7.1				
3 06		7	2.60	23	
3 09	7.4				
3 11		9	1.00	60	
3 17		10	2.28	26	

similar variations. The R-R interval changes quickly with such alterations, lengthening in the less alkaline and shortening in the more alkaline fluid. Figure 2 is a graphic summary of a similar experiment. Table 2 describes an experiment in which the heart was following an idio-ventricular rhythm after all sinus and auricular tissue had been cut away. In this case the rhythm is subject to the same changes in rate following alterations in the reaction of the perfusate. Perfusion with

a solution distinctly less alkaline ( $p_H$  7.0) than the normal ( $p_H$  7.4) resulted in some instances in a total cessation of the heart beat, as shown by the electrical as well as by the mechanical records. This result followed occasionally both with sinus and with the idioventricular rhythms. On return to a solution of  $p_H$  7.4 or 7.8, the beat reappeared almost at once and the rate gradually increased.

It was also possible to control by the same means the rate of propagation of the excitatory process. The figures and tables to which reference

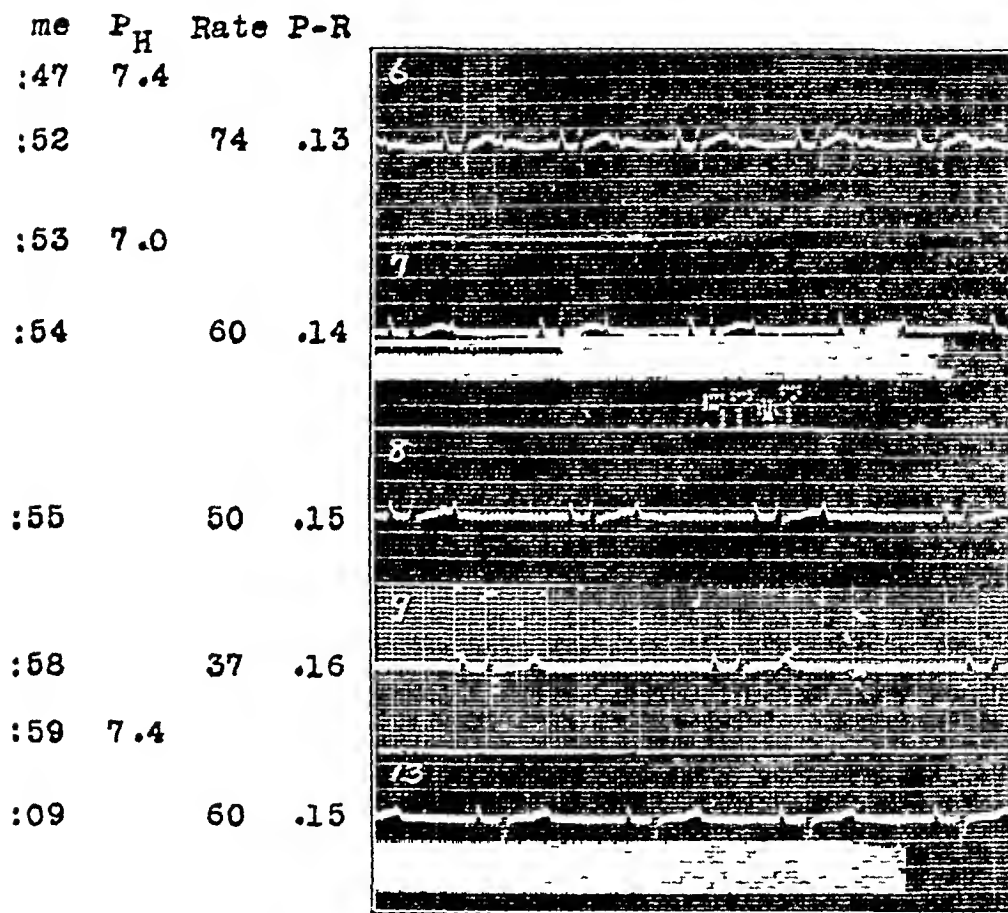


Fig 1—Dog, May 11, 1923. The variations in rate and conduction time following changes in the hydrogen-ion concentration of the perfusate.

has been made show that with more alkaline perfusates the rate of conduction, as measured by the P-R interval, is increased, while with less alkaline fluids it is distinctly retarded. This is especially well shown in Table 1 for the cold blooded heart and in Figures 2 and 3 for the mammalian heart. In the former the rate of spread of the excitatory process over the ventricle, as measured by the Q-R-S interval varies with changes in the  $p_H$  of the perfusate in the same manner as the P-R interval. Since, as Lewis<sup>6</sup> has shown, specialized conducting tissue is

<sup>6</sup> Lewis. Phil Tr Roy Soc London 207 240, 1916

wanting in the tortoise ventricle, prolongation of the Q-R-S interval in this instance must be regarded as due to an effect on the muscular tissue itself. Figure 3 is from an experiment in which two to one auriculoventricular block was induced by a perfusate with  $p_H$  of 7.0 and was later caused to disappear by replacing this with a solution of normal reaction.

From this experimental evidence certain points may be emphasized. Whatever the fundamental process in the development of the cardiac rhythm may be, it takes place more rapidly the more alkaline the fluid

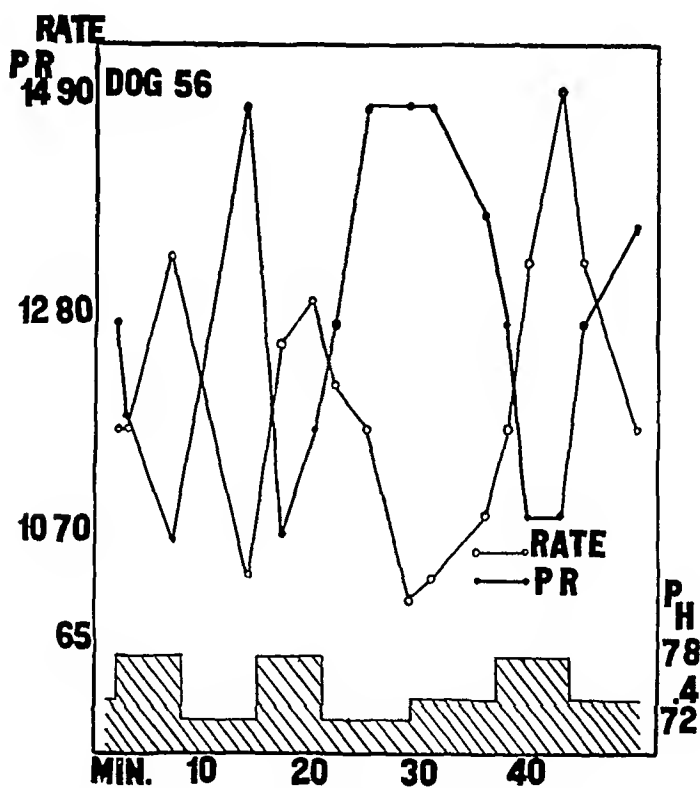


Fig 2—Dog, May 9, 1923. Changes in rate and conduction time with alterations in the reaction of the perfusion fluid.

bathing the tissue of the heart as a whole. Moreover, the rate of excitation is distinctly retarded in the presence of fluid of less alkaline reaction and, when a certain degree of diminished alkalinity is reached, it fails to occur. The propagation of the excitatory process undergoes alteration with varying  $p_H$  in the same sense as its development. These results suggest that for the development of spontaneous excitation in the heart a certain difference in  $p_H$  within and without the tissue must be maintained. That the rate of the rhythm can be varied at will by perfusing with solutions differing only in  $p_H$  is further suggestive evidence in this direction.

## THE RELATION OF ANOXEMIA TO THE CARDIAC MECHANISM

In attempting to apply the hypothesis which has been developed as the result of experimental work to the clinical irregularities of the heart, some functional basis for the changes presumed to take place must be sought. It would appear that a deficient supply of oxygen due to reduction in the local circulatory minute volume is the essential change which

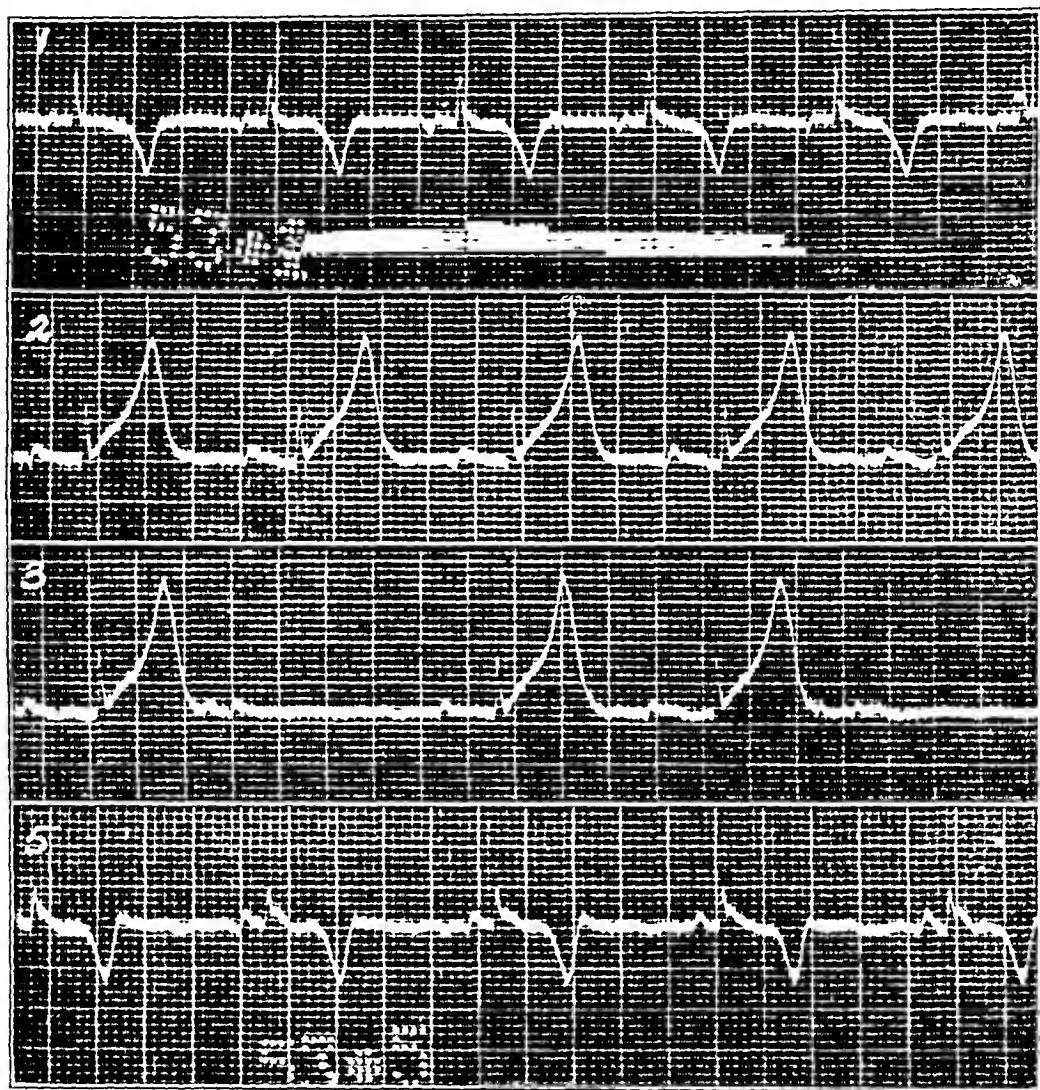


Fig 3—Dog, May 3, 1923. The production of delayed conduction and dropped beats by a perfusate of  $p_{H}$  7.1. 1,  $p_{H}$  7.4, 2,  $p_{H}$  7.1, 3  $p_{H}$  7.1, 5,  $p_{H}$  7.4

may be expected to occur frequently and which might be the underlying disturbance. We have, therefore, examined the meaning of anoxemia from this point of view and gathered together the instances associated with cardiac irregularities. It is not assumed that anoxemia is the sole basis for such disturbances.

Anoxemia may rise through asphyxiation (that is, interference with the supply of oxygen to the pulmonary alveoli) by one means or another,

or through circulatory insufficiency At first glance it would seem that one is dealing with an exceedingly complicated condition, and this is no doubt true from some points of view Nevertheless, the fundamental functional disturbance or internal respiration, which is the essential process at issue, may be regarded as unitary It is well known that the propagation of the excitatory process and the resultant functional response of the tissue to this excitation, for example, contraction, may take place without the immediate consumption of oxygen<sup>7</sup> When contraction occurs under such conditions, lactic acid, which is the end result of the first phase of the process, accumulates within the cell<sup>8</sup> and later possibly in the fluid bathing the cell This results in a local increase in the hydrogen-ion concentration The accumulation of carbon dioxide, which under these circumstances is largely due to the breaking up of alkaline carbonates in the tissue as a result of the increasing acidity,<sup>9</sup> can only produce an enhancement of this effect The rôle of oxygen consists in the removal of lactic acid in part by oxidation, but for the most part by resynthesis into glycogen by a process not at present thoroughly understood<sup>10</sup> Hill and Lupton<sup>11</sup> have applied the results of work of recent years in internal respiration in a study of their relation to conditions in men, which results agree admirably with our knowledge of cellular metabolism They showed conclusively that in exercise an oxygen "debt" is developed through the too rapid accumulation of lactic acid to be removed by the agency of the available oxygen Normally this accumulated lactic acid is satisfactorily "buffered," mainly by tissue proteins In the local breakdown of this mechanism the conditions arise which cause an actual local increase in hydrogen-ion concentration to a level above the normal Such disturbances may take place regionally in relation to the condition of the circulation, and in accordance with the functional activity and buffering power of the tissue It is evident that the heart, being under the necessity of constant activity, may under pathologic conditions suffer such functional disturbances early and frequently Skeletal muscles may be rested or their activity limited, but the heart is dependent on its own activity for the constant restoration of normal conditions by the maintenance of its intrinsic circulation

#### EXPERIMENTAL ASPHYXIA AND ANOXEMIA

The attention of Lewis and Mathison was directed to the relation of general asphyxia to auriculoventricular conduction by observations of

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7 Hill, A. V. *Physiol Rev* 2 310 (April) 1922

8 Fletcher and Hopkins. *J Physiol* 35 247, 1906-1907

9 Fletcher and Brown. *J Physiol* 48 177, 1914

10 Meyerhoff. *Arch f d ges Physiol* 185 11, 1920

11 Hill, A., and Lupton, H. *Quart J Med* 16 135 (Jan) 1923

Sherrington<sup>12</sup> and Roaf and Sherrington<sup>13</sup> As a result, Lewis and Mathison<sup>14</sup> showed conclusively that in cats asphyxiation was soon followed by marked slowing of the sinus rhythm and increase in the conduction time until beats were dropped and finally complete auriculo-ventricular dissociation occurred These disturbances always disappeared on the introduction of a normal supply of oxygen, and took place after section of the vagi and after complete atropinization, as tested by stimulation of the nerves Mathison<sup>15</sup> found that with the vagi intact complete inhibition might occur before heart block appeared He also extended these observations to dogs Robinson and Auer<sup>16</sup> produced progressive auriculoventricular block and bundle branch block in rabbits and dogs by inducing anaphylactic shock with horse serum They also observed indications of a shift of the pacemaker to the auriculoventricular node Some of their experiments were done after section of the vagi, and their results led them to conclude that the changes were not primarily dependent on vagal action There are reasons for believing that the mechanism by which anaphylaxis produces these disturbances depends on local circulatory insufficiency Haggard<sup>17</sup> encountered similar disturbances in dogs, with the respiratory failure which followed carbon monoxid asphyxia He found that there was a temporary period of auricular inhibition which was prevented by the administration of atropin

Greene and Gilbert<sup>18</sup> studied the responses of the circulation in men to gradually reduced oxygen tension by the rebreathing method They found that after a precritical period during which the various compensatory mechanisms dominated the situation, there was great slowing of the rate, shifting of the pacemaker to the auriculoventricular node, and progressive delay in conduction, ending in complete dissociation Following the discontinuance of the rebreathing the normal mechanism was gradually restored in the reverse direction These investigators<sup>19</sup> later used the same method of inducing progressive anoxemia in dogs The same results were secured when the vagi were left intact, but when the vagi were cut, a rapid sinus rate was maintained until the blood pressure manometer failed to record pulse waves, when as a terminal event there was great slowing of the sinus rhythm This and other considerations led Greene and Gilbert to conclude that the distur-

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12 Sherrington J *Physiol* **38** 375, 1909

13 Roaf and Sherrington *Quart J Exper Physiol* **3** 209, 1910

14 Lewis and Mathison *Heart* **2** 47, 1910-1911

15 Mathison *Heart* **2** 54, 1910-1911

16 Robinson and Auer *J Exper Med* **18** 556, 1913

17 Haggard, H W *Am J Physiol* **56** 390 (July) 1921

18 Greene C W, and Gilbert, N C *Studies on the Response of the Circulation to Low Oxygen Tension, Arch Int Med* **27** 517 (May) 1921

19 Greene, C W, and Gilbert, N C *Am J Physiol* **60** 155 (March) 1922

bances described as occurring in experimental asphyxiation and in men exposed to low oxygen tension were due primarily to "vagospasm" and not to local effect of oxygen want. Two objections may be urged to this conclusion. First, the influence of the sympathetic nerves was not eliminated, and second, it is conceivable that they were dealing with the effect of normal vagus action on abnormal local conditions. This question cannot yet be regarded as settled.

#### CIRCULATORY INSUFFICIENCY

Most of the suggestive evidence of the relation of oxygen want to clinical cardiac disturbance is in connection with anoxemia due to general circulatory insufficiency. The most striking instance which seems definite is so-called "asphyxial block." Cases are known of auriculo-ventricular block associated with severe heart failure, in which the normal conduction time has been restored by therapeutic measures which improved the circulation. It is significant that this shortening of conduction time may be accomplished by digitalis.

McCulloch<sup>20</sup> reported in undernourished children, with poor circulation, two instances of abnormally long conduction time which shortened with circulatory improvement. Barach and Woodwell<sup>21</sup> obtained definite improvement of conduction in a case of partial block by the administration of oxygen. Examples of functional interference with conduction through the auriculoventricular bundle are better known. Robinson<sup>22</sup> reported cases showing "aberrant" ventricular complexes following unusually short diastoles, and suggested that the interference with conduction was due to the presence of acid metabolites which were removed by the circulation in the longer pauses. The same author<sup>23</sup> later described a case in which marked heart failure was associated with bundle branch block which disappeared with the improvement following a single large dose of digitalis. Subsequently this patient was seen again with slight heart failure when bundle branch block was present only following short diastolic pauses. Two of Barach's<sup>21</sup> patients showed partial bundle branch block, which disappeared with oxygen therapy. A case similar to that of Robinson, described in the foregoing, is recorded in the files of this laboratory. The patient, when

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20 McCulloch, Hugh. Studies on the Heart in Nutritional Disturbances in Infancy, *Am J Dis Child* **20** 486 (Dec) 1920.

21 Barach, A. L., and Woodwell, M. N. Studies in Oxygen Therapy with Determinations of the Blood Gases, *Arch Int Med* **28** 367 (Oct) 1921.

22 Robinson, G. C. The Relation of Changes in the Form of Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart. *Arch Int Med* **18** 830 (Dec) 1916.

23 Robinson, G. C. The Significance of Abnormalities in the Form of the Electrocardiogram, *Arch Int Med* **24** 422 (Oct) 1919.

first seen, had marked congestive heart failure, and the electrocardiographic record showed typical signs of right bundle branch block with a Q-R-S interval of from 0.14 to 0.16 second. After appropriate therapy, including large doses of digitals, the signs of heart failure disappeared, together with those of bundle branch block. This observation in all its aspects was repeated on the same patient almost a year later. Transient and graded disturbances in bundle conduction in experimental asphyxia have been described by Lewis<sup>24</sup> and are well known clinically.

Recently Gager<sup>25</sup> has described a case of partial heart block in a patient with pericardial effusion. Following treatment, including the removal of the fluid, heart block disappeared completely. The relation of such changes to local circulatory insufficiency is fully discussed, with additional references to the literature.

Electrocardiographic records taken from dying patients furnish us with a series of terminal cardiac disturbances whose basis in most instances is undoubtedly asphyxial. Several observers have reported studies of the events occurring in the hearts of dying patients, showing disturbances of function which agree closely with those encountered in experimental work in which severe anoxemia is produced. Robinson<sup>26</sup> presented a study with electrocardiographic records of the death of seven patients, dying of acute infectious processes without cardiac involvement. Following a preliminary increase in rate, there was consistently a marked progressive slowing of the sinus rhythm. In five patients the conduction time was greatly prolonged and in three of these complete auriculoventricular dissociation occurred. Ventricular fibrillation occurred three times. Halsey's<sup>27</sup> instance of ventricular fibrillation was seen in a patient dying of bronchopneumonia, and preceding this disturbance the records also showed slowing of the sinus rhythm and increase in the conduction time, with the appearance of the signs of partial bundle branch block. Gallavardin<sup>28</sup> reported two instances of long series of ventricular premature beats in dying patients which had not been previously observed. Terminal disturbances of the cardiac mechanism in three patients were described from this laboratory.<sup>29</sup> Much the same changes as those reported by Robinson<sup>26</sup> were found, that is, marked slowing of the rate, increase in the conduction time and in two instances, a shift in the site of the pacemaker, with the development in all three cases of independent ventricular

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24 Lewis. *Heart* **3** 279, 1911-1912.

25 Gager, L. T. Conduction Changes Accompanying Pericardial Effusion, *Arch Int Med* **33** 449 (April) 1924.

26 Robinson. *J Exper Med* **16** 291, 1912.

27 Halsey. *Heart* **6** 67, 1915-1917.

28 Gallavardin, L. *Arch d mal du cœur* **13** 207 (May) 1920.

29 Dieuaide, F. R., and Davidson, E. C. Terminal Cardiac Arrhythmias, Report of Three Cases, *Arch Int Med* **28** 663 (Nov) 1921.



rhythms (long series of premature beats, in one case ending in fibrillation) It was suggested at the time that the underlying pathologic physiology of all these disturbances was probably fundamentally the same In one of the cases there was an interesting example of the presence for a brief time of two noninterfering rhythms in the heart, the first, a much slowed sinus rhythm, and the second an auriculo-ventricular nodal rhythm (Fig 3)

#### CORONARY OCCLUSION

There is one condition in which oxygen want is known to be relatively regional within the heart, namely, interference with the coronary circulation Ventricular rhythms, including single premature beats, paroxysmal tachycardia and fibrillation, have been frequently encountered as a result of both clinical and experimental obstruction of the coronary arteries The work of Lewis,<sup>30</sup> Smith<sup>31</sup> and Robinson<sup>32</sup> shows that this series of ventricular ectopic rhythms, or some one of them, very frequently follows experimental ligation of various coronary branches whether the vagi are cut or not

Robinson and Herrmann<sup>32</sup> observed an instance of paroxysmal tachycardia associated with coronary obstruction, demonstrated at necropsy, and three others in which the diagnosis was made but in which there was no opportunity for its confirmation Longcope<sup>33</sup> described auricular flutter in four out of nine cases in which coronary occlusion was proved The sudden onset of auricular fibrillation, associated with definite symptoms of coronary obstruction, was observed in a patient in this clinic In this instance fibrillation was at first inconstant, being interrupted by periods of normal sinus rhythm and of auricular flutter, but subsequently it became permanent

The inconstancy of such arrhythmias in clinical cases, in which necropsy findings include coronary obstruction, cannot be entirely explained, but in many cases may depend on the particular coronary vessel involved Furthermore, the coronary anastomoses now known to exist would account for the absence of these functional disturbances in some instances, while the changes in the cardiac circulation, which Gross<sup>34</sup> has shown to develop with advancing age, throw some light on the age incidence of severe sequelae of coronary obstruction

In this section an effort has been made to present a summary of the evidence as it exists today, of the relation of oxygen want to cardiac disturbances, together with an interpretation of the local effect of

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30 Lewis Heart 1 98, 1909-1910

31 Smith Arch Int Med 22 8, 1918

32 Robinson, G C, and Herrmann, G R Heart 8 59 (Feb ) 1921

33 Longcope, W T J Iowa M Soc 12 314 (Aug ) 1922

34 Gross Blood Supply of Heart, New York, Paul B Hoeber, 1921

anoxemia from the point of view of internal respiration. There seems to be no doubt that the primary effect of oxygen deficiency in a contractile tissue is to increase the hydrogen-ion concentration. It has been repeatedly observed that anoxemia pushed to a certain point is associated with (1) slowing of the sinus rhythm, (2) interference with conduction, and (3) the appearance of ectopic rhythms.

#### AN INTERPRETATION OF THE CLINICAL DISORDERS OF THE HEART BEAT

Studies of the beat of the heart *in situ* under ordinary circumstances can only furnish suggestive evidence of the effect of variations in hydrogen-ion concentration on the development and propagation of the excitatory process. A consideration of the pathologic physiology involved leads to the conclusion that such variations during life must always be local except in rare and extreme conditions. It is only in recent years and with refined methods that changes in the  $p_H$  of the circulating blood have been detected in other than terminal states. But little is known, as yet, of the relation of such profound general changes to cardiac function. Moreover, abnormalities encountered in the intact heart have to some extent to be interpreted in the light of the control exercised by the extrinsic cardiac nerves. However, it is significant, as Lewis<sup>35</sup> has pointed out, that all of the disturbances in question are encountered in the completely isolated heart. From a general point of view it does not seem that the extrinsic cardiac nerves can play any fundamental rôle in the genesis of the normal or of any abnormal cardiac rhythm, although the action of the vagus and the sympathetic nerves may condition their appearance. Characteristically, the extrinsic nerves exercise but little control over abnormal rhythms, a fact which seems to be correlated with their distribution.

As a profitable basis for their further study and elucidation, it is justifiable to adopt at least tentatively an interpretation of the disturbances of the cardiac mechanism. While the explanation suggested is essentially functional, the part played in many instances by definite anatomic lesions must be borne in mind. At the same time it may be pointed out that in a pathologic process functional disturbance passes gradually into anatomic lesions. Anatomic lesions may interfere with a circulation which in itself is normal.

In the light of the conditions encountered in the clinical observation of cardiac disease, the authors suggest that the conception outlined in the first section of this paper of the nature of the heart beat may assume peculiar significance. The mammalian heart is composed of four types of tissue, nodal tissue, auricular and ventricular muscle, and

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35 Lewis, T. *Quart J Med* 14:345, 1921

Purkinje fibers It has been shown and most recently emphasized by Lewis<sup>36</sup> that these varieties of tissue normally display quantitative differences in function corresponding to differences in structure Dale and Thacker<sup>37</sup> have demonstrated on the heart of the frog that the functional limits, as regard hydrogen-ion concentration, vary in different portions of the heart Similar evidence for the dog's heart has been brought forward by Andrus and Carter<sup>1</sup> These observations are of interest as indicating quantitative differences in the functional response of various portions of the cardiac tissue to changes in the  $p_H$  of the perfusate The normal heart beat represents the coordinated reactions of the various types of tissue

It is universally admitted that the property of inherent rhythmicity is developed to the fullest extent in the specific fibers of nodal tissue To what extent the various other portions of the cardiac muscle mass, excluding the specialized tissue, may be endowed with the function of automaticity is not accurately known It is apparent that under normal conditions such other excitatory centers as may develop lie dormant, giving no evidence of this peculiar property, inherent in all muscle fibers subjected to the proper conditions<sup>38</sup>

Normally, as Gaskell<sup>39</sup> has indicated, the rhythm of the sino-auricular node commands that of the heart as a whole, because its rate is most rapid It is as though local conditions were such that, in a certain portion of the S-A node the membrane equilibriums proceed to the critical level most rapidly and thereupon suffer the displacement which constitutes excitation By virtue of the effect of this local disturbance on the tissue immediately adjacent, the excitatory process is propagated over the auricular muscle toward the ventricle Just above the A-V ring the "propagated disturbance" meets the specialized tissue of the A-V node, wherein local conditions are such that "conduction" is delayed From the A-V node the wave of excitation passes to more specialized tissue in which local conditions, again presumably involving the membrane equilibria are such that the local disturbance incident to excitation is adequate as stimulus over a relatively wide reach of fiber, over the Purkinje system the excitatory process is thus transmitted with extreme rapidity

It is our conception that abnormalities of rhythm, encountered in clinical pathologic conditions, may possibly be explained on the basis of local circulatory deficiency Such an area of deficient blood supply may conceivably involve two factors, inadequate mechanical removal of the products of tissue metabolism, or an insufficient supply of oxygen in

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36 Lewis, T. *Quart J Med* **14** 339 (July) 1921

37 Dale and Thacker. *J Physiol* **47** 493, 1914

38 Mines. *J Physiol* **37** 1908, *Prac Physiol Soc* **1** (May 16) 1908

39 Gaskell. *J Physiol* **4** 43 1883

that area. Under these circumstances one of two conditions may result. An accumulation of waste products (i.e., an increase in hydrogen-ion concentration) in the tissue fluid locally may lead to an area of diminished "conductivity," a localized block. Or, in the event of a more rapid rise in  $p_H$  within the tissue, spontaneous excitation may result in that area, and an "heterogenetic" rhythm may arise. The rate of development of such heterogenetic beats and their duration are dependent on the degree of the local change and on the condition of the cardiac tissue as a whole. A minor disturbance may give rise to extrasystoles which may or may not interrupt the dominant rhythm. A more severe disorder may result in a paroxysm of rapid excitations which for a time command the rhythm of the entire heart. If changes occur which result in a decrease in the refractory period of the tissue or in an interference with the propagation of the excitatory process, the circus movement which has been shown to be at the basis of flutter and fibrillation, may appear.

The conception of the development of a local accumulation of hydrogen-ion giving rise to an interrupting cycle or rhythm does not modify the classification of the cardiac rhythms into homogenetic and heterogenetic types as outlined by Lewis<sup>40</sup>. It cannot be too strongly emphasized that the homogenetic rhythm which governs the heart beating in response to the normal excitation, and that which controls the ventricles in the presence of complete auriculoventricular dissociation arise in the specific nodal tissue. All interrupting rhythms are by their nature heterogenetic in the sense that their origin depends on abnormal conditions in the region in which they arise. This view implies the possibility of the development of heterogenetic foci in nodal and specific bundle tissue.

In connection with heterogenetic rhythms it should be emphasized that an effort to show a fixed rate may lead to confusion. It is true that they are usually fast. It can be demonstrated, however, that, with the exception of auricular flutter, the various heterogenetic rhythms do not always have constant rates, although they are more constant than the homogenetic rhythms. Given constant conditions, the rate of development and discharge of the excitatory process may be very exact, the more rapid it becomes the more exactly rhythmic it appears since the demonstrable error in the cycle length is reduced.

#### SINUS ARRHYTHMIA

We believe that a sinus arrhythmia is determined by the action of the vagus, which so influences the local membrane equilibria as to result in an irregularity in the discharge of the local excitation. The

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40 Lewis. J. Physiol. 4: 321, 1883.

great variation in the rate of stimulus production in the sino-auricular node should be emphasized. Instances of sinus rhythm having a rate as low as 30 have been recorded. It has been shown conclusively that under constant conditions the heart isolated from all sympathetic and vagus connections responds at a constant rate.

#### NODAL RHYTHM

In the extensive literature dealing with the idioventricular rhythm the subject has been treated in great detail from every possible point of view. There is a wide variation in the rates that may be present in complete auriculoventricular dissociation. It has also been shown that in some instances the idioventricular rhythm may have a slightly faster rate than that governing the auricle. Lea's<sup>41</sup> case of complete heart block, in which during a fall to 51 in the sinus rate the ventricular rate rose to 59, is of interest in this connection. In several instances these faster ventricular rates have been induced by drugs,<sup>42</sup> while in others the development of an idioventricular rhythm has been associated with the influence of the extrinsic cardiac nerves.

Heterogenetic rhythms may arise in the auriculoventricular node at a rapid rate, and may even control the auricular systole through retrograde spread of the excitation wave. On the basis of the hypothesis advanced, the occurrence of a nodal excitation implies the development of some local change within the node giving rise to an excitation which is to be regarded as heterogenetic whether this premature contraction interrupts the rhythm of complete heart block or the normal sinus sequence. That there may exist some correlation between the rate of development of the excitation process in the sino-auricular node and the auriculoventricular node seems not improbable. It is apparently true that in some instances in the presence of an extremely slow sinus rate, the inherent periodicity of the auriculoventricular node is correspondingly reduced. There are in this laboratory records of six persons with normal sinus rhythm, in whom the cardiac rate varies from 34 to 46 a minute. In none of these was vagus stimulation followed by ventricular escape.

As further evidence of the inconstant presence of independent rhythmic foci, reference may be made in some detail to the case

<sup>41</sup> Lea. *Lancet* **1** 1289 (Jan) 1915.

<sup>42</sup> Brown, N. W. Sino-Atrial Heart Block in a Child, *Arch Int Med* **24** 458 (Oct) 1919, Gallavardin, Dufourt and Petzetakis, *Arch d mal du cœur* **7** 1, 1914, Hewlett, A. W. *Heart*, **10** 9 (April) 1923, White, P. D. Ventricular Escape with Observations on Cases Showing a Ventricular Rate Greater than that of the Auricles, *Arch Int Med* **18** 244 (Aug) 1916, Wilson, F. N. The Production of Atrioventricular Rhythm in a Man after the Administration of Atropin, *Arch Int Med* **16** 989 (Dec) 1915.

illustrated by Figure 4 *a*, *b*, *c*, and *d*, which affords presumptive proof of the presence of two homogenetic centers dominating at different times the cardiac response, with the occasional occurrence of heterogenetic ventricular beats of a second type. The mechanism involved,

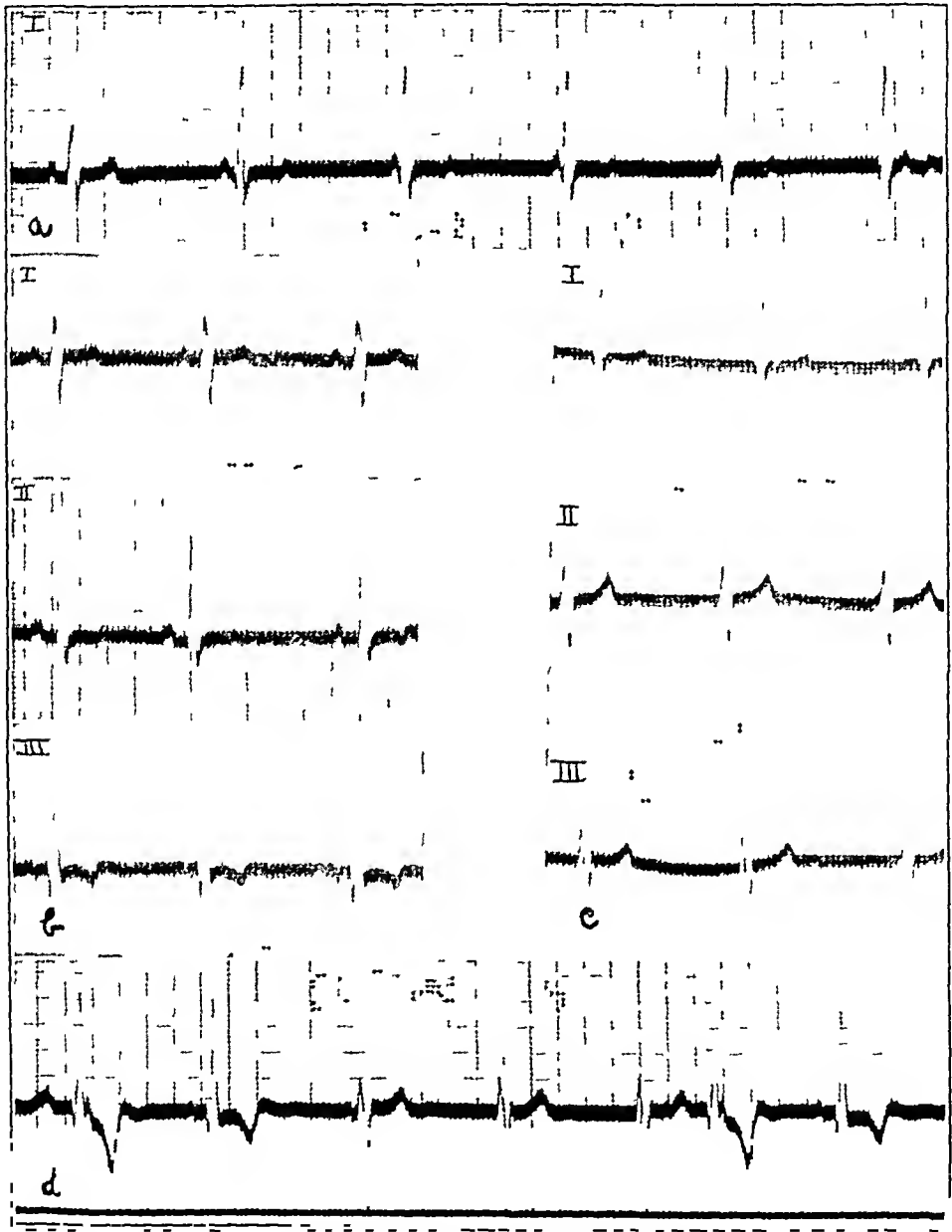


Fig 4—*a*, Lead I. The onset of idioventricular rhythm. *b*, Leads I, II and III. Normal mechanism of case illustrated. *c*, Leads, I, II and III. *d*, Lead III.

as is readily apparent, corresponds in every detail to that seen in the escape of the auriculoventricular node following a progressively slowing sinus rate. In this instance, however, the escape of the subsidiary center is associated, in all three leads, with a ventricular complex that in no way resembles that seen with the normal sinus rhythm. This

subsidiary rhythm can only be interpreted as an escape of the auriculo-ventricular node, constantly associated with an aberrant ventricular complex, or, as due to the presence of a local rhythmic focus at a slightly lower level, lying probably near the point of division of the main His bundle in closer relation to the left than to the right branch. The constancy of the ventricular complex of the ectopic rhythm, together with the extraordinary persistence of the two alternating rhythms, seems wholly to exclude the view that the ectopic rhythm represents an auriculoventricular nodal rhythm with aberrant complexes. Records of this case over a long period, in the entire absence of any digitalis or other drug therapy, show that there is never the slightest variation in the recorded ventricular complexes associated with the two rhythms. Whenever the sino-auricular rate, as determined by the P-P interval, falls to 1 1/2 seconds, the ectopic focus asserts itself and continues at times for long intervals, appearing as in Figure 4 *a*, with a gradually lengthening distance between R and P, or as seen in Figure 4 *c*, as a ventricular rhythm with the P waves of the normal sinus rhythm occurring at the same frequency, lost in the ventricular complex of the ectopic beat. This may be interpreted, it is true, during the interval in which the P wave becomes buried, as an auriculoventricular rhythm with but a single pacemaker. With the presence of the P wave, however, the previous interpretation alone seems possible. Assuming even that there is present a constant shift from an idioventricular rhythm to an auriculoventricular rhythm and back, the inference as to the presence of two rhythmic foci is unaffected. No more striking contrast can be imagined than that illustrated by Figures 4 *b* and *c*. Figure 4 *d* illustrates the occurrence of ectopic ventricular beats of a second type, together with two cycles of the normal sinus rhythm and three cycles of the first ectopic rhythm.

It seems certain that the mechanism involved in this case is of the nature of that present in escape of the auriculoventricular node. The unusual features are the regularity with which the ectopic focus asserts itself in relation to the variable sino-auricular rate, the constancy of the form of the ventricular complex associated with the ectopic rhythm and the persistence of the phenomenon of alternation of the two rhythms from hour to hour and week to week during the entire time the person was under observation. It is of interest that the ventricular extrasystoles are always followed by a cycle of the normal sinus rhythm, and that vagus stimulation is without effect on the ectopic rhythm. It is quite impossible to foretell which of the two rhythms may be in control, while during the activity of the subsidiary ventricular focus the sino-auricular rhythm goes on undisturbed at a slightly slower rate, or apparently synchronously for long periods.

## PREMATURE CONTRACTIONS

It is significant that it has been possible to induce in the isolated perfused heart, interrupting rhythms, as shown in Figure 5, quite as complicated as the clinical arrhythmia illustrated in Figure 6 (discussed further on), with a disappearance of the irregularity on return to an alkaline perfusate

The occurrence of extrasystoles having a constant form, can be regarded as evidence of a local automatic focus only when they appear

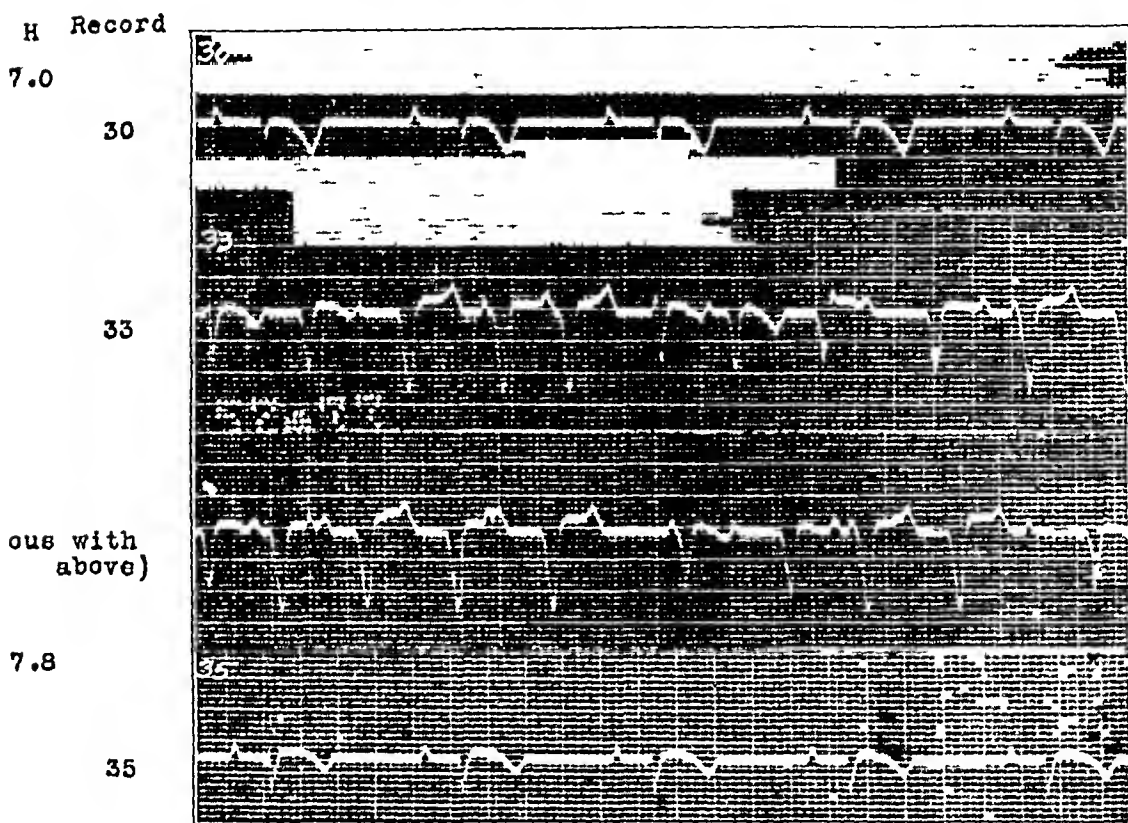


Fig 5—Dog, May 11, 1923 The production of ventricular premature beats by an acid perfusate and their disappearance on return to an alkaline perfusate

so long after the preceding cycle that they cannot possibly be interpreted as re-entrant waves. That under some conditions premature beats may be due to the re-entry of the preceding excitatory process of the dominant rhythm must be admitted. Although an isolated extrasystole can in no sense be interpreted as evidence of a rhythmic focus, under the conditions defined above it represents a focus of automaticity which may declare itself by continuous cycles arising rhythmically. When single extrasystoles appear from time to time in a person known to have attacks of multiple runs of similar complexes, then and then only can such a single interrupting cycle be considered as representing



a rhythmic focus, though the isolated interrupting cycles are not to be regarded as members of a continuous rhythm. This distinction we believe to be fundamentally important.

In the analysis of the galvanometric curves of clinical cases the interpretation of the location of the abnormal focus is made solely on the difference in form of the interrupting complex from that of the normal rhythm. On this account the interpretation of a sinus extrasystole may remain incapable of proof.<sup>43</sup>

Many observers<sup>44</sup> have published curves illustrating the incidence of single and even multiple premature auricular complexes, which are interpreted as arising nearby or within the sino-auricular node. Of the origin of extrasystoles arising within the auriculoventricular node there is abundant and demonstrable evidence. By analogy it is difficult to question the occurrence of sino-auricular extrasystoles. It seems a justifiable inference that under certain conditions of local circulatory change a focus in the sino-auricular node, other than that giving rise to the dominant rhythm, may develop an excitatory process. Under these circumstances the interrupting focus should be considered as nomotopic but heterogenetic. We believe that it is the development of such foci within the sino-auricular node that results in what has hitherto been described as a "shift of the pacemaker within the sino-auricular node" as in the experimental curves of Lewis'<sup>45</sup> dogs. The vagal mechanism involved in such an experimental shift does not come within the scope of this discussion.

It should be emphasized that it is held by some observers that there is no evidence of the active existence of two rhythms in the same chamber of the heart at the same time. There is, however, evidence supporting the view that at least two foci of automaticity may be present in the same chamber at the same time. In this connection the instance reported by Klewitz<sup>46</sup> is of unusual interest and it is difficult to escape the conclusion based on the published curves, that there were two conflicting

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43 Belski. *Ztschr f klin Med* **67** 515, 1909, Lohmann. *Arch f Anat u Physiol (Physiol Abth)* **431**, 1904, Rihl. *Deutsch Arch f klin Med* **94** 286, 1908, Rihl. *Ztschr f exper Path u Therap* **9** 496, 1911, Ritchie. *Quart J Med* **6** 47, 1912, Rothberger, C. J. *Klin Wchnschr* **1** 2150 (Oct) 1922, Rothberger, C. J., and Winterberg. *Arch f d ges Physiol* **142** 461, 1911, Wenckebach. *Arch f Anat u Physiol (Physiol Abth)* Supp **1** 53, 1908.

44 Carter, E. P., and Wedd, A. M. Report of a Case of Paroxysmal Tachycardia Characterized by Unusual Control of the Fast Rhythm, *Arch Int Med* **22** 571 (Nov) 1918, Klewitz. *Centralb f Herz u Gefasskh* **12** 54, 1920, Lewis, Thomas. Mechanism and Graphic Registration of the Heart Beat. London, Shaw and Sons, p 229, 1920, Wenckebach. *Arch f Anat u Physiol (Physiol Abth)* **1**, 1907, White, P. D. Clinical Observations on Unusual Mechanisms of the Auricular Pacemaker, *Arch Int Med* **25** 420 (April) 1920.

45 Lewis, Meakins, and White. *Phil Tr Roy Soc, London* **205** 375, 1914.

46 Footnote 44, second reference.

hythms present in the sino-auricular node during the same period. It is of additional significance in connection with its origin that the heterogenetic rhythm could be abolished by vagal stimulation and, therefore, must have arisen in an area supplied by the vagus.

As evidence of the effects of local or regional changes within the auricle, one has but to recall the frequency with which heterogenetic auricular beats occur, which are capable of interpretation by the character of their recorded curves, by their time relationship to the dominant rhythm and in many instances by the alteration in conduction time.

The occurrence of ventricular premature contractions which fulfil the conditions imposed in the foregoing, offers the simplest proof that the underlying disturbance is essentially a local one. These subordinate heterogenetic rhythms develop at a wide range of periodicity, and under certain conditions the frequency of the subordinate focus may show an apparent relationship to that of the controlling sinus rhythm. The idea that a relationship exists between the normal sinus rhythm and a subordinate rhythmic focus, as evidenced by the occurrence of

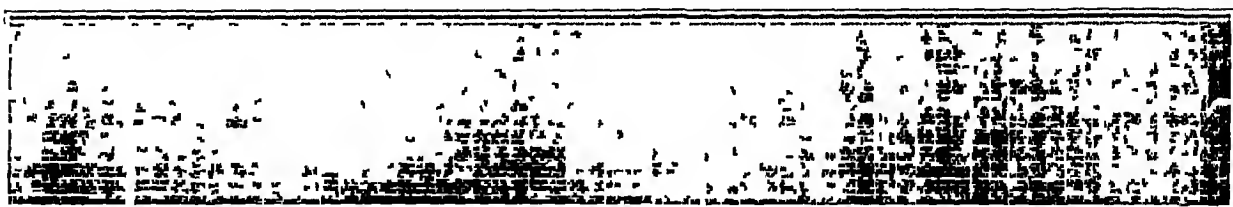


Fig 6—Lead I. Two series of premature beats from different foci. The normal P waves occur independently of the ectopic beats.

extrasystoles at definite time intervals, has been developed in an interesting way by Kaufmann and Rothberger.<sup>47</sup> The recent study by Iliescu and Sebastiani<sup>48</sup> to show that no such relationship can be established does not seem conclusive. The question of the relationship of the ectopic rhythm to the dominant rhythm in the presence of coupled beats is a very difficult one. That the extrasystole is induced by the normal systole, even in those instances in which there is a strikingly constant time interval between the sinus beat and the coupled cycle, has not yet been proved. Under these conditions, however, the question of an alteration in the refractory period of the heart muscle and the possibility of re-entry of the excitation wave must be emphasized. The appearance of the second cycle may be conditioned by the normal cycle but its genesis is determined by regional processes.

An example of three independent rhythmic foci, the normal sinus and two ectopic ventricular rhythms, is illustrated in Figure 6. Each

<sup>47</sup> Kaufmann, R., and Rothberger, C. J. *Klin Wchnschr* **1** 1840 (Sept) 1922.

<sup>48</sup> Iliescu, C. C., and Sebastiani, A. *Heart* **10** 101 (April) 1923.

of the two subsidiary foci breaks through at different times with its own periodicity, while the normal sinus rhythm can be spaced throughout the curves uninfluenced by the rate of the heterogenetic centers. The rhythms of these heterogenetic foci are not continuous, nor can their appearance be predicted. Each focus, however, when it does appear, has a rate which tends to be characteristic. Thus the normal sinus rhythm is interrupted frequently by a rhythm arising in the ventricles having a rate of 182, with a duration occasionally of at least 30 cycles. This tachycardia is in turn replaced by a rhythm from a second ventricular center at a rate of 88 while throughout the tachycardias the normal P wave appears at its own inherent frequency of 93.

#### CIRCUS MOVEMENTS

The "circus movement," which underlies auricular flutter and fibrillation, has a direct bearing on the theory offered in explanation of the genesis of the cardiac beat only in that the functional alterations involved in the establishment of this process are conceivably determined by diffuse circulatory changes of the sort described. Following immediately on the establishment of a circus movement, however, the evidence of the point of origin of the excitatory process is lost. The auricular complexes only afford a measurement of the rate at which the excitatory process, in its spread through the auricular tissue, passes a given point. The theory suggested does not modify in any way the present conception of the evolution of circus movements, but on the other hand aids in our conception of the development of local areas of muscle bundles through which the passage of the excitatory process is delayed. It is important to remember the significance of the refractory period of the heart in connection with re-entrant waves of excitation. The possible effect of a change in the hydrogen-ion concentration on the refractory period of cardiac muscle offers a problem of the greatest significance to the hypothesis advanced. We have frequently observed in experimental fibrillation of the ventricles that there are many local areas of conflicting, re-entering waves quite apart from the chief circus movement. Finally it is important that there is no evidence that a circus movement may not be initiated by the dominant rhythm, its onset being determined by primary changes in the refractory period due to disturbances in membrane equilibria.

#### SUMMARY

The hypothesis that the "automaticity" of the heart is due to the rhythmic displacement of the membrane equilibria is advanced as applicable to the cardiac arrhythmias. It is suggested that the development of the excitatory process is determined by the difference in hydrogen-ion concentration within the cardiac tissue and in the tissue fluid bathing it.

Normally, the spontaneous development of the excitatory process takes place only in the sino-auricular node, but it may, by a process relatively normal, readily occur, usually at a slower rate, in the auriculo-ventricular node. These mechanisms constitute the homogenetic rhythms. The excitatory process is propagated through the effect of the local disturbance on the membrane equilibria in adjacent tissue, an effect also controlled by the  $p_H$  within and without the tissue.

It is further suggested that under pathologic conditions local accumulation of hydrogen ions may develop in nodal tissue or in various other parts of the heart, giving rise to heterogenetic beats or rhythms, the evidence for this is outlined. Re-entrant waves and circus movements may be accounted for by regional or diffuse changes of the same nature. The mechanism by which pathologic changes usually produce these results is a local increase in hydrogen-ion concentration within the tissue, which is due to an insufficient supply of oxygen. On the other hand, a pathologic process which causes a relative increase in the concentration of hydrogen ions in the tissue fluid interferes with the spread of the excitatory process, thereby giving rise to the various forms of "block." The mechanism of these general type of pathologic processes is discussed and experimental and clinical instances suggestive of their operation are described.<sup>49</sup>

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49 Since this paper was written, two of us (E P C and F R D) have completed a study, to be reported in detail later, demonstrating that in the perfused dog's heart the refractory period of the cardiac muscle varies with the  $p_H$  of the perfusion fluid, being lengthened on the acid side and shortened on the alkaline side of neutrality. Andrus and Drury, in a series of observations soon to be reported, have further demonstrated that when the dog's auricle is perfused with oxygen-free Locke's solution of  $p_H$  7, there results a condition in which the transmission of the excitation becomes progressively slower the farther the wave travels from its point of origin. If such perfusion is continued, partial or complete block may be produced within the auricular muscle itself. Such a condition bears a striking similarity to the phenomenon described in the nerve as "conduction with a decrement."

# THE AMINO-ACID CONTENT OF BLOOD IN VARIOUS PATHOLOGIC CONDITIONS

AN ANALYSIS OF ONE HUNDRED AND SIXTY DETERMINATIONS  
ON ONE HUNDRED AND TWENTY PERSONS \*

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AND

ISRAEL SHAPIRO, B A

BROOKLYN

Basing the study on an analysis of the results obtained in 160 routine determinations of the amino-acid nitrogen in the blood of 120 subjects, mostly patients with miscellaneous pathologic conditions, an attempt has been made here to correlate the abnormal findings with any diseases with which they might consistently be associated. With reference to conditions in which other investigators have found high figures for the amino-acids of blood, our cases were grouped for separate study in order to show at a glance what our findings have been in these conditions. Finally, the tabulation was studied with a view to ascertaining a possible relationship between retention of urea nitrogen and accumulation of amino-acids in the blood. A small group of amino-acid nitrogen readings from fluids other than whole blood is appended.

Folin,<sup>1</sup> in a group of twelve normal young men, found the average value of amino-acid nitrogen in whole blood to be 6.4 mg per hundred cubic centimeters, with a maximal reading of 7.8 mg, and a minimal reading of 5.7 mg. In his opinion, the deamination process is so fundamental that one cannot expect to find many pathologic conditions in which the aminonitrogen of the blood filtrates will vary very much from the normal.

In acute yellow atrophy of the liver, the amino-acid nitrogen of the blood was found by Stadie and Van Slyke<sup>2</sup> to be greatly increased. Okada and Hayashi,<sup>3</sup> in 1922, obtained pronounced rises in the blood aminonitrogen in cases of leukemia, the figures being approximately proportioned to the white cell count. In five cases of splenomyelogenous

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\* From the Clinical Laboratory, United Israel Zion Hospital.

1 Folin, O. Laboratory Manual of Biological Chemistry, 1922, p. 279, New York, D. Appleton & Company.

2 Stadie, W. C., and Van Slyke, D. D. The Effect of Acute Yellow Atrophy on Metabolism and on the Composition of the Liver, Arch. Int. Med. 25: 693 (June) 1920.

3 Okada, S., and Hayashi, T. Studies on the Amino-Acid Nitrogen Content of the Blood, J. Biol. Chem. 51: 121 (March) 1922.

TABLE 1—Findings in a Group of One Hundred and Twenty Patients

Case	Mg per 100 C c Blood Filtrate		Diagnosis
	Amino Acid Nitrogen	Urea Nitrogen	
1	17.5	37.5	Cardiac decompensation, myocarditis
2	16.4	15.0	Emphysema
	9.3	15.0	
	5.8	13.6	
3	12.0	42.8	Coronary sclerosis, pulmonary tuberculosis
4	12.0	12.0	Stillbirth, mother eclamptic
5	11.0	171.2	Uremia, nephrolithiasis
	6.8	171.2	
6	10.0	30.0	Diabetic coma
7	10.0	15.4	Colitis
	9.1		
	8.2		
	6.4		
8	9.3		Lobar pneumonia
	8.7		
	8.7		
	8.2		
	5.8		
9	8.7	15.0	Chronic cholecystitis
	7.0	15.0	
10	8.7	20.6	Chronic myocarditis
11	8.7	12.0	Carcinoma of stomach
12	8.5		Infective cholangitis
	7.0		
	7.0	24.9	
13	8.2		Normal
	7.9		
	7.9		
14	8.2	15.0	Diabetes mellitus
15	8.2	13.4	Diabetes mellitus
	7.3	16.7	
16	8.2	15.6	Cholelithiasis
17	8.2	50.0	Chronic glomerular nephritis, uremia
18	8.2	13.6	Cerebral thrombosis
19	8.2	15.0	Carcinoma of pancreas
20	8.0		Normal
21	7.9		Syphilis of liver
	7.9		
	7.0		
22	7.7	15.0	Cerebrospinal syphilis
23	7.7	15.2	Pyelitis
24	7.6	12.0	Ureteral obstruction
25	7.7		Acute gangrenous appendicitis
26	7.4	14.6	Herpes zoster
27	7.4	17.6	Diabetes mellitus
28	7.4	30.0	Diabetes mellitus
29	7.4		Acute nephritis
30	7.4		Rheumatic fever
31	7.2		Tuberculous pleurisy, osteo arthritis
32	7.2		Diabetes mellitus
	7.0	15.4	
	5.2		
33	7.2	15.8	Arteriosclerosis, abdominal angina
	7.0	15.8	
	7.0	16.8	
	7.0	15.0	Coronary sclerosis
34	7.0	15.8	Parturition
35	7.0		Menopause
36	7.0		Ovarian cyst
37	7.0	15.8	Myocardial insufficiency
38	7.0	15.8	
	7.0	15.0	
39	7.0		Normal
	6.7		
	6.1		
40	7.0	27.2	Constipation
41	7.0	18.8	Cerebral arteriosclerosis
42	7.0		Chronic colitis
43	7.0		Osteo arthritis
	6.6		
	6.4		
	6.4		
44	7.0	18.8	Coronary sclerosis
45	7.0	15.0	Multiple myositis
46	7.0	17.6	Mitral stenosis
47	7.0	13.6	Diabetes mellitus
	6.6		
48	7.0	14.4	Cholecystitis
49	7.0	15.8	Pneumothorax
50	7.0		Hyperthyroidism
51	7.0	15.8	Chlorosis
52	7.0	15.0	Ureteral obstruction

TABLE 1—*Findings in a Group of One Hundred and Twenty Patients—(Continued)*

Case	Mg per 100 C e Blood Filtrate		Diagnosis
	Amino Acid Nitrogen	Urea Nitrogen	
53	7.0	18.8	Auricular fibrillation
54	7.0	21.3	Lobar pneumonia
55	7.0	15.8	Acute infectious arthritis
56	7.0	15.8	Diabetes mellitus
	6.4	18.8	
	5.0		
57	7.0	15.0	Hydronephrosis
58	7.0	15.0	Umbilical hernia
59	7.0		Renal calculus, hydronephrosis
60	7.0	27.2	Food allergy
	7.0		
	7.0		
61	7.0	15.0	Diabetes mellitus
62	7.0		Osteo arthritis
63	7.0		Osteo arthritis
	5.6	15.8	
64	6.8	16.7	Pregnancy, epilepsy
65	6.7		Carbuncle
66	6.7		Diabetes mellitus
	5.4	15.8	
67	6.6		Influenzal pneumonia
68	6.6	15.8	Neurasthenia
69	6.6	21.4	Cerebral arteriosclerosis
70	6.6	15.8	Diabetes mellitus, hepatic cirrhosis
71	6.6	27.2	Ureteral obstruction
72	6.6	55.0	Chronic glomerular nephritis, uremia
73	6.6	12.0	Eclampsia
74	6.6		Diabetes mellitus
75	6.6	15.0	Diabetes mellitus
	6.4	15.0	
76	6.6		Acute nephritis
77	6.5	17.6	Typhoid fever
78	6.4	17.6	Acute nephritis
79	6.4	20.6	Hypertrophied prostate
80	6.4		Diabetes mellitus
81	6.4	14.4	Diabetes mellitus
82	6.4	15.8	Ventral hernia, peritoneal adhesions
83	6.4	15.8	Menopause
84	6.4	15.0	Peritoneal adhesions
85	6.4	15.0	Bronchopneumonia
86	6.4	15.0	Diabetes mellitus acute cholecystitis
	5.8		
87	6.4	15.0	Endarteritis obliterans
88	6.4		Parturition
89	6.4		Diabetes mellitus
90	6.4	17.6	Rheumatic fever
91	6.4	12.5	Rheumatic fever
92	6.4	16.7	Acute polyarthritis
93	6.3	15.8	Cardiac decompensation
94	6.3	15.8	Arteriosclerosis, hepatic cirrhosis, osteo arthritis
95	6.3	15.8	Myocardial insufficiency
96	6.3		Diabetes mellitus
97	6.3	15.0	Tuberculous pleurisy, osteo arthritis
98	6.2	16.7	Cerebral hemorrhage
99	6.1	15.8	Influenzal pneumonia
100	6.1	16.7	Arteriosclerosis, myocarditis
	6.1		
101	6.1	30.0	Chronic glomerular nephritis
102	6.1	15.8	Gastric ulcer
103	6.1	27.2	Rheumatic fever
104	6.1	13.7	Parturition
105	6.0		Chronic glomerular nephritis
106	5.8		Epidemic meningitis
107	5.8	15.8	Infective cholangitis
109	5.8		Chronic glomerular nephritis, uremia
	5.2	60.0	
109	5.8	16.7	Undetermined
110	5.8	37.5	Multiple abscesses of kidney, chronic cholecystitis
111	5.8	17.6	Encephalitis, hypertrophied prostate
112	5.8	15.0	Lobar pneumonia
113	5.8	16.7	Traumatism to kidney
114	5.8	17.6	Acute cholecystitis
115	5.6	15.0	Hypertrophic cirrhosis
116	5.4	15.8	Diabetes mellitus
117	5.4		Subacute bacterial endocarditis
118	5.3	15.8	Aortitis and myocarditis
119	5.0	15.0	Lobar pneumonia
120	4.0		Diabetes mellitus

leukemia studied by Sandiford, Boothby and Giffin,<sup>4</sup> the amino-acid nitrogen blood values ranged from 5 to 16 mg per hundred cubic centimeters, with an average of 10 mg

Desqueyroux,<sup>5</sup> in 1923, studied the amino-acids and other nitrogen products in the blood of forty patients and three healthy persons, and he obtained increased values for the amino-acid nitrogen of blood in diabetes mellitus, nephritis with nitrogen retention, myocardial insufficiency and pneumonia. In pathologic conditions of the liver, irregular readings were obtained. On the contrary, Green, Sandiford and Ross,<sup>6</sup> in 1924, made 458 observations covering twenty pathologic conditions and they found that the amino-acid nitrogen in the blood is maintained within normal limits with remarkable constancy and that such disease as uremia, diabetes, exophthalmic goiter and hepatic insufficiency furnish no exception to the rule.

In our study, the specimens of blood were drawn before breakfast, and the amino-acid nitrogen was determined according to Folin's<sup>7</sup>

TABLE 2—*Amino-Acid Nitrogen in Blood in Conditions Reputed to be Associated with Hyperamino-Acidermia*

Diagnosis	No. of Cases	Amino Acid Nitrogen in Whole Blood, Mg. per 100 Cc.		
		Minimum	Maximum	Average
Diabetes mellitus	20	4.0	10.0	6.7
Chronic glomerular nephritis	5	5.5	8.2	6.5
Uremia	4	5.5	8.9	7.3
Hepatic cirrhosis	3	5.6	6.6	6.2
Normal	3	6.6	8.0	7.5

NOTE.—Where more than one determination was made, the average of all the readings in that case was taken.

colorimetric method, the urea nitrogen determinations were made by Folin's<sup>8</sup> urease colorimetric method.

In Table 1 we have enumerated in order, according to the amino-acid nitrogen values, our findings as to this substance and urea nitrogen in the blood of a group of 120 patients, representing a total of 160 examinations.

Assuming 8.5 mg per hundred cubic centimeters to represent an abnormal level for the amino-acid nitrogen of blood, a perusal of Table 1 will show that the first twelve cases exhibited excessive values.

4 Sandiford, K., Boothby, W. M., and Giffin, H. Z. The Amino-Acid Nitrogen in the Blood and Its Possible Relations to the Elevation of the Metabolism in Myelogenous Leukemia, *J. Biol. Chem.* **55** 23, 1923.

5 Desqueyroux, J. Recherches cliniques sur l'hyperamino-acidémie, *Ann. de méd.* **13** 20 (Jan.) 1923.

6 Green, C. H., Sandiford, K., and Ross, H. The Amino-Acid Content of the Blood in Normal and Pathologic Conditions, *J. Biol. Chem.* **58** 845 (Jan.) 1924.

7 Folin, O. Laboratory Manual of Biological Chemistry, 1922, p. 259.

8 Folin, O. Laboratory Manual of Biological Chemistry, 1922, p. 239.



for this substance From a study of this table, it at once becomes apparent that no special conditions within this series were consistently associated with hyperamino-acidemia

In Table 2 are enumerated the disease conditions to which high values of amino-acid in blood have been attributed, together with our findings in these same conditions

In our series, consistently high readings were not found in diabetes mellitus, chronic glomerular nephritis, uremia or cirrhosis of the liver An occasional high reading was obtained, but, in many instances, subsequent examinations gave normal figures No attempt is made to interpret the individual high readings in the light of the diagnosis, on the contrary, our findings have failed to show a consistent association between hyperamino-acidemia and any pathologic condition

In one instance, parallel observations were made on the blood of an eclamptic mother and that of a stillborn infant, the latter specimen being taken from the placental end of the umbilical cord very shortly

TABLE 3—Comparative Figures for Urea Nitrogen and Amino-Acid Nitrogen in Sixteen Specimens with Urea Nitrogen Values Exceeding 25 mg per 100 c c

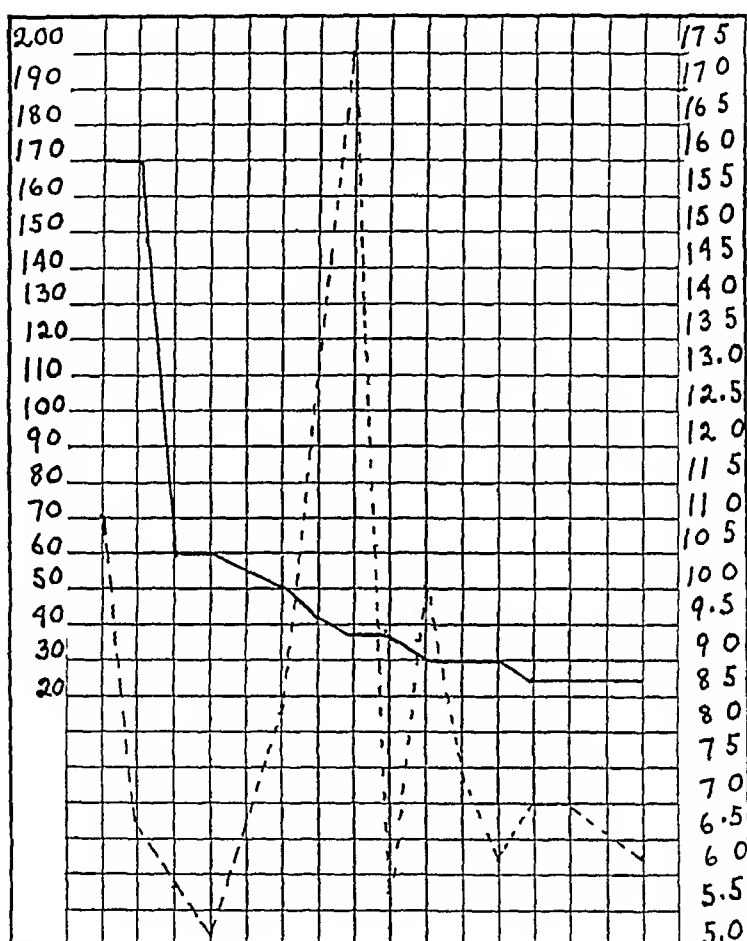
Mg per 100 C c of Blood		Mg per 100 C c of Blood	
Urea Nitrogen	Amino Acid Nitrogen	Urea Nitrogen	Amino-Acid Nitrogen
171.2	11.0	37.5	5.8
171.2	6.8	30.0	10.0
60.0	5.8	30.0	7.4
60.0	5.2	30.0	6.1
55.0	6.6	27.2	7.0
50.0	8.2	27.2	7.0
42.8	12.0	27.2	6.6
37.5	17.5	27.2	6.1

after the death of the fetus The fetal blood had an amino-acid nitrogen value almost twice that of the mother, rating 12 mg per hundred cubic centimeters as against 6.6 mg Higher values for amino-acids in the blood of the new-born infant appear to be the rule In eighteen comparisons made by Morse,<sup>9</sup> in 1917, the reading was higher in the fetal blood in thirteen instances, lower in one, and identical readings were obtained in four cases

Having in mind a possible relationship between retention of urea nitrogen and high amino-acid figures in the blood, we have grouped in Table 3 all of those cases which showed a reading in excess of 25 mg of urea nitrogen per hundred cubic centimeters, and have concurrently tabulated the amino-acid figures A study of these results shows that, while in an individual instance urea retention is apt to be accompanied

9 Morse, A The Amino-Acid Nitrogen of the Blood in Cases of Normal and Complicated Pregnancy and Also in the New-Born Infant, Bull Johns Hopkins Hosp 28 199 (June) 1917

by hyperamino-acidemia, this association is just as often completely lacking. As graphically represented in the chart, there was a marked absence of parallelism between the respective levels of urea nitrogen and of amino-acids in blood. Even when an abnormally high reading for amino-acids is obtained, it is not constant. Thus, in Case 5 (Table 1), the values of urea nitrogen and amino-acid nitrogen per hundred cubic centimeters of blood were 171.2 mg and 11 mg respectively, a subse-



Concurrent readings of the amino-acid nitrogen of blood in sixteen cases in which the urea nitrogen readings were in excess of 25 mg per hundred cubic centimeters, showing the lack of parallelism between the values for the two substances. The left hand figures refer to the urea nitrogen values in terms of milligrams per hundred cubic centimeters and the solid line gives the respective values for this substance in the cases cited. The right hand figures refer to the amino-acid nitrogen values in terms of milligrams per hundred cubic centimeters, and the interrupted line gives the respective values for this substance in the same cases.

quent examination yielded the same reading for urea, but the amino-acid nitrogen had dropped to 6.8 mg.

Our findings in this respect are in accord with those of Green, Sandiford and Ross,<sup>6</sup> who found no apparent correlation between the

amino-acids and the degree of renal insufficiency or urea retention. Experimentally, Haden and Orr,<sup>10</sup> in 1923, produced intestinal obstruction in dogs, but although there was a marked increase in the blood urea, no change occurred in the amino-acid nitrogen content of the blood.

In Table 4 there are tabulated four comparative amino-acid readings between the blood and some other fluid.

TABLE 4—*Comparative Readings of Amino-Acid Nitrogen in Blood and in Other Fluids*

Fluid	Mg per 100 C c	Blood	Mg per 100 C c	Diagnosis
Bile	14.6	6.6		Cerebral arteriosclerosis
Spinal fluid	4.6	10.0		Diabetic coma
Lung fluid	8.1	16.0		Diabetic coma
Chest fluid	5.6	7.0		Myocardial insufficiency

#### SUMMARY

An analysis of 160 amino-acid nitrogen determinations in blood on 120 patients failed to indicate any pathologic conditions with which abnormally high values for this element are consistently associated. In the twelve patients whose bloods gave readings in excess of 8.5 mg per hundred cubic centimeters, no causal relationship between the malady and the hyperamino-acidemia was apparent. Furthermore, a study of twenty cases of diabetes mellitus, five of chronic glomerular nephritis, four of uremia, and three of hepatic cirrhosis, showed the average amino-acid nitrogen value in blood to be normal in all of these conditions, although individual instances of increased readings occurred in the first three groups. Abnormally high values frequently returned to normal in subsequent examinations. In a group of sixteen tests in which the urea nitrogen value of the blood exceeded 25 mg per hundred cubic centimeters, there was concurrent elevation of the amino-acids in only four instances, and even then there was no parallelism between the two substances. No cases of leukemia or of acute yellow atrophy of the liver were included within this study.

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<sup>10</sup> Haden, R. L., and Orr, T. G. Chemical Changes in the Blood of the Dog After Intestinal Obstruction, *J. Exper. Med.* **37** 365 (March) 1923, Chemical Changes in the Blood of the Dog After Pyloric Obstruction, *J. Exper. Med.* **37** 377 (March) 1923.

# STUDIES ON ACUTE INTESTINAL OBSTRUCTION

## II ACUTE STRANGULATION \*

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In the preceding paper <sup>1</sup> we have shown that acute intestinal obstruction may be divided both clinically and experimentally into acute simple obstruction and acute strangulation, that the symptomatology, length of life and lethal factors are different in each case. In uncomplicated simple obstruction death is probably due to starvation and its sequelae.

In this paper we report a series of experiments demonstrating that the foregoing factors in simple obstruction play little or no part in acute strangulation but instead that death is due to shock and toxemia. The rapidity with which these factors act varies with the length of intestine involved, the degree of arterial and venous obstruction and the location of the lesion.

No attempt will be made to review the extensive literature on the subject of intestinal obstruction. Only those articles which have dealt with experimentally produced strangulation will be briefly summarized. Von Albeck <sup>2</sup> was the first to produce experimental strangulation. He used loops from 6 to 8 inches (from 15 to 20 cm) in length. His dogs died in collapse in from twenty-four to forty-eight hours, showing vomiting, diarrhea, subnormal temperature and spasms prior to death. He concluded death was due to the absorption of putrefactive toxins formed in the strangulated loop.

Eisberg <sup>3</sup> also produced strangulation but under morphin ether anesthesia. In his animals the minimum length of life was from three to seven hours, the maximum duration forty-two hours. His statements are rather indefinite and not detailed. In speaking of the cause of death he says "Surely at times a devitalized segment appears to be responsible for a lethal outcome, long before there has been time for bacterial action to play a part in the results."

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1 Hausler, R W, and Foster, W C. Studies in Acute Intestinal Obstruction. I. Different Types of Obstruction Produced under Local Anesthesia. Arch Int Med **34** 97 (July) 1924

2 Von Albeck. Arch f klin Chir **65** 569, 1902

3 Eisberg, H B. Ann Surg **74** 584 (Nov) 1921

Murphy and Vincent <sup>4</sup> are the only other authors who have paid any particular attention to circulatory conditions in obstruction. Their work was on cats. Strangulation, venous obstruction and anemia were produced under ether anesthesia. Blood pressure tracings under ether anesthesia were taken by them on the carotid artery at irregular intervals. Such procedures have many disadvantages and introduce other factors, especially in a very sick animal. To quote them further, "the animals after from four to six hours were in such poor condition that it was difficult to etherize them and obtain a second reading, since the slightest excess of ether was fatal, and the low blood pressure tended to the formation of a clot in the cannula." The local anesthesia method used on the femoral artery in our series permits of hourly tracings with no inconvenience to the dog, and excludes vagal and sympathetic stimulation and ether intoxication. Murphy and Vincent report that with venous obstruction the height of intoxication was reached in from four to six hours. They believe the symptoms and death to be due to "bacterial endotoxemia."

#### MATERIAL AND METHODS

The operative detail has been given in a previous paper. All operations were performed on dogs under local anesthesia with careful aseptic technic. Definite lengths of bowel were twisted and tied with rubber tubing in such a way as to cause a complete venous obstruction. Temperature, pulse, respiration and blood pressure were taken before and at definite intervals after operation. Blood chemistry estimations were made in the chemical laboratory. All solutions were adequately checked. The following methods were used: Blood sugar, Haskins-Holbrook <sup>5</sup> modification of Shafer titration method, total nitrogen, Microkjeldahl, urea nitrogen, Microkjeldahl, chlorids, Folin <sup>6</sup>.

The dogs were kept under almost continuous observation from the beginning of the experiment until death. Necropsies were performed immediately. The abdominal organs were fixed and sectioned for microscopic examination.

#### EXPERIMENTAL OBSERVATIONS

From the first series of twelve dogs with acute strangulation the following five typical protocols illustrate the postobstructive course when different lengths of the intestine are involved.

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4 Murphy and Vincent. Boston M & S J 165 684, 1911.

5 Haskins, H. D., and Holbrook, W. P. J. Lab & Clin. Med. 8 747 (Aug.) 1923.

6 Folin O. K. Lab. Manual of Bio. Chem. Ed. 2, 1919.

## PROTOCOL OF EXPERIMENTS

EXPERIMENT 1—Dog 50, adult, tan terrier, male, weight, 23 pounds (10 kg) Five inch (127 cm) segment Death in twenty-nine hours

10 05 a m Temperature (rectal), 102.4 F, pulse, 84, respirations, 20, blood pressure, 150 systolic

10 15, operation Five inches (127 cm) of jejunum and ileum strangulated Off table 10 30 Ran about the room

12 00 noon Temperature, 101.8, pulse, 110, respirations, 24, blood pressure, 146 systolic Animal in good condition Drank and vomited at frequent intervals

2 00 p m Temperature, 98, pulse, 130, respirations, 28, blood pressure, 144 systolic Whined frequently and seemed distressed

5 00 p m Temperature, 99.2, pulse, 130, respirations, 28, blood pressure, 140 systolic Howled frequently and was very nervous

7 30 a m Next day Temperature, 104.4, pulse, 190, respirations, 36, blood pressure, 110 systolic, the dog appeared to be very toxic and vomited frequently

10 30 a m Temperature, 104.6, pulse, 190, respirations, 34, blood pressure, 90 systolic Hardly able to walk

2 00 p m Temperature, 105.6, pulse, 210, respirations, 68, blood pressure, 50 systolic Dog moribund

3 15 p m, the dog was killed, and there was an immediate necropsy Findings Lungs, liver, spleen and kidneys were grossly normal Peritoneal cavity contained considerable foul smelling fluid Strangulated segment was ruptured, purplish black in color and necrotic Generalized peritonitis

EXPERIMENT 2—Dog 53, brown female, weight, 30 pounds (13.6 kg) Twelve inch (30 cm) segment Death in twenty-five hours

4 15 p m Temperature, 101.4, pulse, 84, respirations, 18, blood pressure, 145 systolic

4 30 p m Operation Strangulation of 12 inches (30 cm), upper ileum Off table at 4 50 Walked to cage, few minutes later vomited

9 00 a m Following day Temperature, 101.6, pulse, 152, respirations, 26, blood pressure, 130 systolic The animal looked sick Frequent vomiting after drinking Gait steady

11 00 a m Temperature, 101.6, pulse, 164, respirations, 28

12 00 noon Temperature, 102.4, pulse, 200, respirations, 27, blood pressure, 120 systolic The dog appeared much weaker

1 30 p m Temperature, 103, pulse, 220, respirations, 32 The animal was still able to walk

2 40 p m Temperature, 102.4, pulse, 210, respirations, 36, blood pressure, 98 Much weaker

3 45 p m Temperature, 104.4, pulse, 210, respirations, 48, blood pressure, 80 Dog lay in the cage, unable to stand

4 45 p m Temperature, 105.8, pulse, 280, respirations, 70, blood pressure, 50 systolic

5 20 p m Dead Immediate necropsy Findings Peritoneal cavity contained about 300 c.c. of dark, bloody, foul smelling fluid, the strangulated loop was ruptured Other viscera were grossly normal

EXPERIMENT 3—Dog 56, adult female collie, weight, 28 pounds (12.7 kg) Fifteen inch (37 cm) segment Death in twenty-two hours

10 45 a m Temperature, 102.8, pulse, 72, respirations, 18, blood pressure, 160 systolic

11 00 a m Operation Fifteen inches (37 cm) of lower ileum strangulated Off table at 11 20 Ran about room

2 30 p m Temperature, 105.6, pulse, 74, respirations, 72, blood pressure, 152 systolic There was marked thirst and frequent vomiting during the last two hours

5 00 p m Temperature, 104.4, pulse, 84, respirations, 42, blood pressure, 145 systolic

9 00 p m Temperature, 104.6, pulse, 160, respirations, 24, blood pressure, 124 systolic Dog looked dejected, marked thirst and much vomiting

8 00 a m Following day Temperature, 107, pulse, 240, respirations, 56, blood pressure, 74 systolic

9 00 a m Dead Necropsy at once Necropsy findings Gangrenous, strangulated loop ruptured, belly full of bloody exudate, tissue very friable Generalized peritonitis Other viscera were grossly normal

EXPERIMENT 4—Dog 35, white bull, male, weight, 22 pounds (10 kg) Eighteen inch (45 cm) segment Death in ten hours

8 30 a m Temperature, 101.8, pulse, 94, respirations, 18, blood pressure, 152 systolic, white blood count, 6,900

9 15 a m Operation Eighteen inches (45 cm) of upper ileum strangulated Off table at 9 35 Ran around room Whined, drank and vomited a few minutes later

9 50 a m Temperature, 101.6, pulse, 160, respirations, 20, blood pressure, 150 systolic

10 40 a m Temperature, 101.6, pulse, 162, respirations, 20, blood pressure, 118 systolic Vomited frequently, very thirsty

12 00 noon Temperature, 99.1, pulse, 160, respirations, 22 Dog very listless Vomited blood-stained bowel contents

2 20 p m Temperature, 101, pulse, 180, respirations, 21, blood pressure, 102 systolic Animal markedly shocked Still able to walk, staggering gait

4 20 p m Temperature, 101.2, pulse, 180, respirations, 22, blood pressure, 88 systolic Hardly able to walk, fell frequently Respirations irregular and loud Drank occasionally and retched

5 05 p m Temperature, 99.6, pulse, 180, respirations 26, blood pressure, 71 systolic Advanced stage of shock

7 06 p m Temperature, 99.6, pulse, 178, respirations, 26, blood pressure, 62 systolic, white blood cells, 10,700 No response to sensory stimuli

8 05 p m Dead Necropsy immediately Findings Lungs, liver, spleen and kidneys were grossly normal Strangulated segment enormously distended, glistening black in color, contained 150 cc of dark bloody fluid, only slight odor Stomach, duodenum and large intestine very anemic Forty cubic centimeters of blood stained fluid in the peritoneal cavity

EXPERIMENT 5—Dog 36, adult Airedale male, weight, 30 pounds (13.6 kg) Twenty-four inch (60.96 cm) segment Dead in seven hours

10 30 a m Temperature, 102.2, pulse, 84, respirations, 16, blood pressure, 138 systolic, white blood count, 14,500

11 30 a m Operation Twenty-four inches (60.96 cm) of lower ileum strangulated Off table at 11 42 Ran about room, appeared normal

11 50 a m Temperature, 102.6, pulse, 100, respirations, 26 Very thirsty, drank, vomited in a few minutes

1 00 p m Temperature, 101.5, pulse, 170, respirations, 26, blood pressure, 120 systolic Stuporous and dazed

3 00 p m Temperature, 101.4, pulse, 180, respirations 36, blood pressure, 88 systolic Dog weaker, when forced to get up staggered and leaned against cage for support Respirations rapid and stertorous

3 40 p m Temperature, 101.4, pulse, 182, respirations, 42, blood pressure, 44 systolic Gradually getting weaker

4 50 p m Temperature, 101.4, pulse, 220, respirations, 46, blood pressure, 42 systolic Profound shock

6 00 p m Temperature, 100.2, pulse, 228, respirations, 46, blood pressure, 42 systolic, white blood count, 18,400

6 30 p m Dead Necropsy findings Abdominal and thoracic viscera grossly negative Strangulated visceral segment distended, gangrenous, con-

tained 35 cc of dark, bloody fluid. Fifty cubic centimeters of similar fluid were found in the peritoneal cavity. No perforation.

Table 1 shows that there is a direct relationship between the length of bowel strangulated and the rapidity with which death ensues.

Naturally slight variations occur, due to the size and the type of the dog and the degree of venous occlusion produced at operation. However, the results definitely indicate that the longer the segment, the more pronounced the shock and the earlier the death. With the short segments, 12 inches (30 cm) or less, shock although present, is not sufficient to cause a pronounced derangement and disorganization of the cardiovascular mechanism. The fall in blood pressure is only moderate, the pulse rate is not extremely rapid and the animals are able to overcome this primary phase, only to succumb later to a terrific toxemia and peritonitis. In the cases with long segments, 18 inches (45 cm) or more, shock appears very early and is extremely severe. The blood

TABLE 1—*Relationship Between Length of Bowel Strangulated and Death*

Dog No	Weight in Pounds	Inches of Bowel Strangulated	Length of Life, Hours
50	23	5	29
60	42	6	28
53	30	12	25
37	26	12	24
34	17	12	23 5
56	28	15	22
40	35	15	20
31	50	18	12
35	22	18	10
32	47	24	9
36	30	24	7
39	35	26	8 5

pressure falls rapidly, the pulse rate climbs to a very high level and the temperature falls. The animal goes into collapse and dies from shock before toxemia can develop.

#### TOTAL ANEMIA

In this group, segments of bowel from 12 to 20 inches (from 30 to 50 cm) in length were used. Three of the loops were found perforated at necropsy. This group does not parallel any clinical entities, but serves as a check on other observers' experiments. The following typical protocol well represents this series, of four dogs, in which the intestine was tied so tightly that a complete and instantaneous anemia was produced.

EXPERIMENT 7—Dog 38, adult mongrel male, weight, 35 pounds (15 kg). Twenty inch (50 cm) segment. Dead in twenty hours.

10 30 a m. Temperature, 102.8, pulse, 90, respirations, 16; blood pressure, 146 systolic, white blood count, 8,900.

11 00 a m. Operation. Total anemia of 20 inches (50 cm) of upper ileum. Off table at 11 20. Dog vomited two minutes after leaving the table.



12 00 noon Temperature, 102.8, pulse, 140, respirations, 20, white blood count, 11,600 The animal vomited frequently and appeared distressed Blood pressure, 134 systolic

2 30 p m Temperature, 101.3, respirations, 28, pulse, 140, blood pressure, 125 systolic Frequent vomiting Gait steady, condition fair

7 00 p m Temperature, 102.9, pulse, 140, respirations, 36, blood pressure, 115 systolic, white blood count, 10,500 Condition somewhat weaker but presented none of the marked shock symptoms seen in the previous series No further observations were made during the night

7 00 a m Temperature, 98.6, pulse, 240, respirations, 40, blood pressure, 38 systolic Dog moribund

7 35 a m Dead Immediate necropsy Findings Lungs, spleen, kidneys and liver grossly normal Peritoneal cavity contained small amount of blood stained fluid Strangulated segment was slightly distended with gas Pale, yellowish, pasty substance in the bowel lumen Tissue of segment very friable, of a yellowish color, showed no perforation

In this group it is obvious that the pathologic and the clinical pictures are entirely different from those of venous obstruction The total anemia intestine shows little or no dilatation and contains no fluid On the other hand, with venous obstruction the strangulated loop is dilated to two or three times its normal size and enormously distends the abdominal cavity Furthermore, this group, in which there is no blood or fluid loss and only slight distention of intestine, does not show the acute collapse symptoms of the venous obstruction series Instead, we have only a slight, gradual rise in pulse rate and a practically normal blood pressure during the first fifteen hours Vomiting is less profuse, thirst slight, and the animal is much stronger The temperature and respirations, however, show extreme elevation, which are not seen in the strangulation animals The respiratory rate always rises in a few hours to 40 or 50 per minute, and in one case it averaged 120 per minute for over sixteen hours The temperature shows a gradual continuous rise to an average maximum of 105 during the last five to eight hours

The above experiments prove (1) that in acute strangulation blood loss and loop distention are important factors in the production of shock, (2) that a rapid rise in respiration and temperature, along with only slight variations in pulse rate and blood pressure, are indicative of toxemia and peritonitis

#### RUBBER BAG SERIES

In order to show the relative importance of toxemia and shock in acute strangulation, five dogs were treated as follows At operation the bowel segments were introduced into thin rubber bags, and a rubber catheter was tied around the base sufficiently tight to cause complete venous obstruction This procedure prevents the absorption of toxins from the strangulated segment by the peritoneal serosa, without interfering with the distention of the segment by blood and gas

EXPERIMENT 8—Dog 12, black and white mongrel, male, weight, 31 pounds (14 kg) Twenty-four inch (60 cm) segment Dead in eight and one-half hours  
9 00 a m Temperature, 102.6, respirations, 20, blood pressure, 145 systolic, white blood count, 14,200

9 30 a m Operation Twenty-four inches (60 cm) of upper ileum and jejunum strangulated in rubber sac Off table in twenty minutes Drank freely, vomited

10 00 a m Temperature, 102.6, pulse, 95, respirations, 24, blood pressure, 145 systolic

11 00 a m Temperature, 102.6, pulse, 200, respirations, 30 Dog drank, retched and vomited frequently and appeared weaker

12 00 noon Temperature, 102.6, pulse, 240, respirations, 36, white blood count, 20,600 Frequent whining and vomiting.

1 05 p m Temperature, 102.8, pulse, 240, respirations, 50, blood pressure, 86 systolic Animal rapidly going into shock, leaned heavily against cage

2 30 p m Temperature, 102.3, pulse, 250, respirations, 42, blood pressure, 68 systolic Dog very weak, in collapse

3 30 p m Temperature, 104.3, pulse, 250, respirations, 48, blood pressure, 68 systolic, white blood count, 9,200

4 45 p m Temperature, 104.6, pulse, 250, respirations, 52, blood pressure, 62 systolic Could hardly walk When aroused dog stood up and then fell

5 30 p m Temperature, 104.6, pulse, 260, respirations, 48, blood pressure, 40 systolic Moribund

6 08 p m Dead Immediate necropsy Findings Peritoneum normal, small amount of fluid present No perforation Intestine was greatly distended with gas and contained 250 cc of dark, bloody fluid Gallbladder contained 20 cc concentrated fluid Proximal intestine empty and anemic, of mottled appearance

EXPERIMENT 9—Dog 13, adult mongrel, male, weight, 30 pounds (13 kg) Ten inch (25 cm) segment Death in Sixty-six hours

March 9, 2 00 p m Temperature, 102.8, pulse, 86, respirations, 20, blood pressure, 150 systolic

2 30 p m Operation Ten inches (25 cm) of jejunum strangulated in rubber sac Off table in twenty minutes

5 00 p m Temperature, 102.8, pulse, 110, respirations, 24, blood pressure, 145 systolic Occasional vomiting Condition good

March 10, 8 00 a m Temperature, 102.6, pulse, 96, respirations, 26 Dog appeared in excellent condition, wagged tail, walked about with no difficulty Respirations were slightly labored

2 00 p m Frequent vomiting, appeared weaker

March 11, 8 30 a m Temperature, 103.2, pulse, 108, respirations, 26 Animal in good condition

5 00 p m Temperature, 104, pulse, 130, respirations, 28, blood pressure, 138 systolic Dog looked toxic

March 12, 8 00 a m Dog moribund Killed Necropsy findings Sac distended with gas and contained about 100 cc bloody fluid Perforation just proximal to tie Generalized peritonitis

In the foregoing experiments long and short loops were used From the previous experiments it was evident that shock was the predominating lethal factor when long segments were used Thus the use of the rubber bag to prevent any possible absorption should not materially effect the duration of life A comparison of Experiment 4 (segment 24 inches, death in seven hours) with Experiment 8 (segment 24 inches placed in rubber sac, death in eight and one-half hours) shows that

the change in temperature, pulse, respiration, blood pressure and duration of life are practically identical in each case. It is thus evident that toxemia is only of minor importance, since the prevention of the absorption of toxin does not materially affect the outcome. With short loops, however, where toxemia is more predominant and shock of a milder degree, the length of life should be markedly affected. A comparison of Experiment 2 (segment 12 inches, death in twenty-five hours) with Experiment 9 (segment 10 inches, in rubber bag, death in sixty-six hours) reveals this difference in a very striking manner. The foregoing experiments prove the following: (1) In the rapidly fatal cases of long segment strangulation toxemia is not an important lethal factor, (2) in the short segments toxemia is very pronounced.

#### RELEASE OF STRANGULATION

To show the effect of release of the strangulation after shock symptoms had become moderately advanced experiments of the following nature were performed:

EXPERIMENT 14—Dog 47, adult brown male, weight, 50 pounds (22 kg)

11 00 a m Temperature, 101.2, pulse, 62, respirations, 16, blood pressure, 146 systolic

11 45 a m Operation Strangulation of 20 inches (50 cm) of upper ileum. Off table in fifteen minutes. Vomited slight amount of blood tinged mucus. Voided 175 cc urine. Small stool.

12 45 p m Temperature, 97, pulse, 50, respirations, 28, blood pressure, 132 systolic. Dog appeared to be very sick. Whined continuously, seemed cold. Heater placed in cage.

2 00 p m Temperature, 104.7, pulse, 206, respirations, 30, blood pressure, 100 systolic. Condition worse.

2 55 p m Temperature, 105, pulse, 184, irregular, respirations, 32, blood pressure, 78 systolic. Anal sphincter relaxed.

4 00 p m Temperature, 106, pulse, 170, respirations, 42, blood pressure, 75 systolic. Appeared deeply shocked, hardly able to stand.

4 20 p m Belly opened under local anesthesia, strangulation relieved. Gut appeared very black, apparently not viable, but returned to belly cavity without resection.

5 45 p m Temperature, 106, pulse, 172, respirations, 40, blood pressure, 84 systolic. Passed small liquid stool twenty minutes after removal of strangulation. Given one grain morphin by hypodermic.

6 45 p m Temperature, 106.5, pulse, 170, respiration, 50, blood pressure, 90 systolic. Frequent small, fluid stools. Sleeping quietly.

7 30 p m Temperature, 105.2, pulse, 210, respiration, 50, blood pressure, 95 systolic. Five hundred cc of 5 per cent glucose in physiologic sodium chlorid solution given subcutaneously. Condition much improved.

April 11, following day

8 00 a m Temperature, 103.2, pulse, 100, respirations, 24, blood pressure, 115 systolic. Dog appeared to be in good condition.

From this time the recovery was uneventful.

This animal was sacrificed one week later. The segment previously strangulated was markedly thickened, hard and indurated and mottled purplish in color. Lumen patent but smaller than normal. Peritoneum smooth and glistening, with no signs of adhesions.

These experiments illustrate very clearly the degree of systemic depression produced by the violent peristalsis of the proximal segment and the stretching of both the parietal and visceral peritoneum by the strangulated intestine. These loops are always distended to about two or three times their former length and diameter, completely filling and distending the peritoneal cavity.

Before the release of the obstruction the animals were in a precarious condition. The blood pressure was low, the pulse rapid and feeble, respirations fast and stertorous, and muscular weakness was pronounced. The dogs were hardly able to stand, and paid little attention to external stimuli.

As soon as the obstruction is released a marked change occurs. The animal is visibly relieved, the depression passes, vomiting ceases and the bowels are emptied by two or three liquid stools. He is soon able to walk about and drinks large quantities of water. Soon the pulse becomes slower and of a better quality. The temperature returns to normal. The blood pressure and respirations show few changes during the first three hours. The following day the animal is in a good condition and usually makes an uneventful recovery. The loop fluid, which was always allowed to pass into the distal segment, produces a mild diarrhea, but apparently without any marked deleterious effect on the animal.

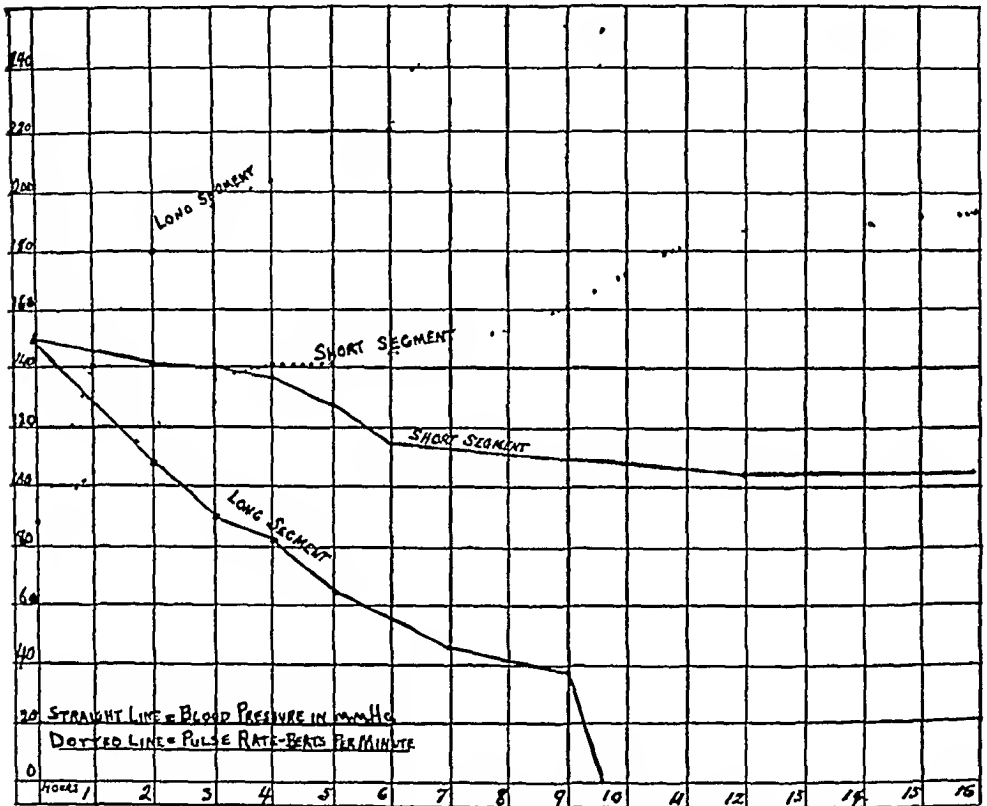
The foregoing results further indicate that shock is a predominating lethal factor in early strangulation. Toxemia apparently has not developed to any marked degree. Further discussion of these experiments will be given in a subsequent article on the treatment of acute intestinal obstruction.

#### OBSERVATIONS ON PULSE AND BLOOD PRESSURE

One of the most outstanding features of acute strangulation experimentally produced is a constant, pronounced fall in blood pressure, and a coincident and proportionate increase in pulse rate. These striking observations are graphically presented in the chart. A definite relation exists between the length of segment strangulated and the blood pressure and the pulse changes. In the long segments a rapid fall in blood pressure from an average of 150 mm of mercury systolic to 90 mm occurs within the first three hours. At the end of five hours it has dropped to 60 mm and by seven hours has usually reached the 40 mm level. At the same time the pulse rate jumps from an average of 80 to 90 per minute to about 140 at the end of the first hour, 180 or above at the end of two hours, 200 at four, and from there on until death it averages about 240 beats.

In short segments the blood pressure falls to approximately 110 mm systolic in the first six hours and remains at about this level until

several hours before death. At this time a very rapid fall begins, often amounting to 60 mm in an hour's time. The pulse rate usually shows a fairly rapid rise within the first six hours to an average of 140 per minute. After this level has been reached there is generally only a slight elevation during the next ten hours. After sixteen hours, however, a profound toxemia has developed and the pulse shows a rapid increase to over 200, at which level it continues until death.



Composite curves of pulse and blood pressure variations in long and short segment strangulation

#### TEMPERATURE

The temperature in acute strangulation is so subject to fluctuation that it does not give a reliable indication of the pathology or condition of the experimental animal. Some dogs with long strangulated segments, profound shock and early death show a temperature curve that does not vary over one-half a degree from the normal. Others, with exactly similar pathology, have a rapid fall of three or four degrees within the first two hours. In general, however, the longer segments show a slight fall at the end of two hours and then a more rapid progressive decline until death. The blood pressure and temperature curves are very similar in time and extent. In short segments there is

little or no variation within the first ten hours. After this time, however, a marked toxemia or peritonitis has developed, and the temperature is usually very high, averaging about 105 F.

The clinical value of external heat applications was well demonstrated in several cases of profound shock, a subnormal temperature of 97 F, rising in an hour's time to 103 F with marked improvement in the animal's general condition.

#### RESPIRATION

In all cases of acute strangulation there was a definite increase in respiratory rate. The curve parallels that of the pulse rate very closely. In the long segment cases there is an early rise from a normal of approximately 20 to an average of 44 per minute. They usually become shallow and thoracic in type, and toward the last are very irregular. With the shorter segments there is an early increase of about ten respirations per minute, at which level it remains until the onset of profound toxemia, when a rapid elevation to 40 or more takes place.

#### TOXICITY OF LOOP AND PERITONEAL EXUDATES

Much work of a very technical nature has been done on the chemistry and toxicity of the loop fluid in dogs in which no circulatory disturbances were produced. The degree of toxicity was determined for the most part by intravenous injection of loop content, but since the normal bowel contains many proteoses and amines which are very toxic on intravenous injection, too much weight cannot be placed on the results of such experiments. There can be no question about the toxicity of body fluids and bowel content when these are mixed with bacteria and left in a virtual incubator for twelve hours or more. This is evidenced in the peritonitis following bowel rupture, in which cases death ensues in a relatively short time from a terrific toxemia.

The purpose in the following experiments was to determine the relative toxicity of the loop content of dogs dying in less than twelve hours, and to ascertain its relation to the sudden collapse beginning two or three hours after strangulation, to which certain authors refer as a profound toxemia.

In acute strangulation, obstruction of the venous and lymphatic channels is produced by the constricting band and the subsequent thrombosis of the mesenteric vessels. Thus the only possible path of absorption is by a transudation of the loop fluid through the strangulated bowel walls into the peritoneal cavity and thence by the peritoneal lymphatics into the blood stream. Further, the inflammatory reaction of the peritoneal serosa to this transudate may partially detoxicate it. Therefore, it seemed unphysiologic to inject this fluid intravenously,

and accordingly in the following experiments we have made all injections intraperitoneally. The fluid was drained from the strangulated segments immediately after death, filtered through sterile gauze to facilitate injection, and without further treatment, either by heat or chemicals, injected intraperitoneally. By this simple treatment any increase or decrease in toxicity by necropsy changes was prevented.

In the first experiment a mixture of the loop fluids of Dog 32, dying in nine hours, and Dog 31, dying in twelve hours, was injected into a normal, young dog, weighing 12 pounds (5.4 kg), with the results seen in Table 2.

TABLE 2—*Experiment 16, Dog 33, Young Mongrel, Male, Weight 12 Pounds (5.4 kg)*

Time	Temperature	Respiration	Pulse	Amount of Fluid
6 30 p m	103.0	16	90	Normal
6 40 p m	103.0	16	90	20 c c
7 30 p m	102.8	22	96	20 c c
8 30 p m	102.4	28	110	20 c c
9 00 p m				20 c c
Next day				
8 15 a m	104.0	34	180	No injection

The dog showed signs of peritonitis for a few days but made an uneventful recovery.

In order to test the toxicity of early loop fluid in massive doses the entire loop contents, 100 c c, of a dog dying in seven hours (Experiment 5, Dog 36), was injected in one dose, with the result seen in Table 3. The fluid was left on ice over night.

TABLE 3—*Experiment 17, Dog 38, Young, Black and White, Male Mongrel Weight 15 Pounds (6.8 kg)*

Time	Temperature	Respiration	Pulse	Amount of Fluid
9 30 a m	103.4	20	100	Normal
9 45 a m	103.4	20	100	104 c c
1 20 p m	103.3	28	134	
4 00 p m	104.0	28	160	
Next day				
9 00 a m	103.1	30	120	
11 00 a m	103.2	26	118	

Half an hour after the injection the dog showed marked salivation, dry nose and restlessness, and vomited once. Two hours later he appeared depressed, but walked about quite normally. After six hours the condition was much improved. On the following day the dog was in good condition, and made an uneventful recovery. An exploratory laparotomy on this animal three weeks later revealed a normal peritoneal serosa.

In dogs dying from experimental strangulation there is always a bloody exudate found at necropsy in the abdominal cavity. The total quantity of this fluid was gathered from one dog (Dog 31, dying in

twelve hours), 60 c c in amount, and injected intraperitoneally with the results seen in Table 4

About two hours after the injection the dog appeared slightly depressed. He held his belly rigid and the respirations were shallow and thoracic in type. The nose was dry and he drank freely. He passed one liquid stool. The following day the animal appeared entirely normal.

In the preceding experiments no attempts were made to kill the bacteria in the loop fluid before its injection into the experimental animal. Accordingly, part of the reaction obtained is undoubtedly due to the subsequent peritonitis following this massive bacterial injection. The fact that no severe peritonitis followed demonstrates the enormous ability of the peritoneum to overcome bacterial invasion. All of the injected animals were small and young, and therefore, if the fluid was very toxic, should have shown extreme reaction to these doses.

The process of transudation from the strangulated intestine and absorption via the peritoneal serosa is a gradual one, beginning soon

TABLE 4—*Experiment 18, Dog 37, Brown, Mongrel, Male, Weight 11 Pounds (5.0 kg)*

Time	Temperature	Respiration	Pulse	Amount of Fluid
10 35 a m	103.2	22	120	Normal
10 40 a m				60 c c
11 05 a m	103.4	22	110	
1 30 p m	101.4	26	110	
3 35 p m	103.5	28	80 Irreg	
6 00 p m	103.0	22	62	
Next day				
8 00 a m	102.3	18	60	

after the strangulation is produced. The amount of this transudation varies at different times, according to the pressure within the strangulated loop and the force of the incoming arterial flow. In the first experiment, therefore, amounts similar to what might have been absorbed were given at hourly intervals. Since the reaction was very slight and no great degree of toxicity was evidenced in the first animal, the second animal was given the entire loop contents in one massive dose. This procedure gave a more pronounced reaction, but this animal likewise quickly recovered. The free peritoneal fluid, which is a mixture of transudate and peritoneal exudate, proved to be relatively nontoxic.

The preceding protocols show that the fluids which accumulate in the peritoneal cavity and strangulated loops of less than twelve hours' duration are not highly toxic when introduced intraperitoneally, even in massive doses. Furthermore, they indicate that the sudden and extreme collapse following long segment strangulation cannot be explained entirely as a profound toxemia.



## BLOOD CHEMISTRY

Table 5 shows the changes in blood urea, nonprotein nitrogen, sugar and chlorids in five of the strangulation dogs

It will be seen that there is an increased nonprotein nitrogen in all cases. The final determinations, however, are not far above the normal level. They probably indicate both urinary retention and increased tissue destruction. Urea nitrogen also consistently increases, but does not always parallel the nonprotein nitrogen curve. Blood sugar shows marked fluctuations, usually within normal limits, at no time was there a definite continuous hypoglycemia or hyperglycemia. In two dogs the sodium chlorid percentage is decreased slightly, in two a slight

TABLE 5—*Blood Chemistry in Five Dogs*

Dog No	Hours After Operation	Blood Chemistry, Amounts per 100 C c				Length of Life
		Total Nonprotein Nitrogen, Mg	Urea Nitrogen, Mg	Sugar, Mg	Sodium Chlorid, Mg	
36	0	28	9.6	114	501	7 hours
	7	50	22.4	66	501	
32	0	30	19.0	101	478	9 hours
	4		23.0	173		
	6		25.0	150	412	
	7	42	31.0	90		
	8		29.0	137		
	9	60	36.0	114	379	
35	0	32	9.8	98	462	10 hours
	6			129		
	10	42	18.3	85	501	
31	0	28	11.5	104	478	12 hours
	3		16.5	95		
	5		16.0	78		
	6		17.0	86	495	
	7		26.5	91		
	8	28	25.0	98		
	9	35	26.0	82		
	10	28	24.0	114	501	
37	0	22	12.0	81	500	24 hours
	6	24	14.0	92	470	
	12	30	19.0	67	445	

increase was noted, and in the other there was no change. The chlorid variations apparently have little significance.

Immediately after the strangulation is produced, violent peristalsis begins in the proximal segment and in five to fifteen minutes is followed by intense retching and vomiting. The character and frequency of vomiting and the type and amount of vomitus vary at different stages. At first it contains the typical stomach content, acid in reaction, not bile stained and composed largely of a watery fluid mixed with partially digested food. This primary vomiting gives only short relief and is soon followed by smaller amounts of bile-stained alkaline material, evidently the content of the bowel between the stomach and the point of obstruction.

After this initial cleansing of the proximal intestine has been completed the frequency of vomiting and the character and amount of vomitus depends entirely on the fluid intake. If the dogs are allowed to drink all of the water they desire, the vomiting is very frequent, from every ten to fifteen minutes, profuse in amount and consisting entirely of a clear, watery mucus, alkaline in reaction. At first sight it seems evident that the dogs are losing a large quantity of fluid by profuse intestinal secretion and this undoubtedly accounts for the prevalent belief that death in obstruction is due to dehydration. An accurate measurement of the fluid intake and the amount of vomitus shows, however, that the two are practically identical. Over 90 per cent of the vomitus is ingested water and the remainder is thick, mucous intestinal secretion. Thus, with each attack of emesis the animal does not lose more than from 10 to 20 c c of fluid.

On the other hand, if the dogs are allowed no fluids by mouth the picture is greatly altered. The frequency of vomiting is markedly decreased, usually occurring only about once an hour. However, when the vomiting spells do come on they are much more severe, consisting almost entirely of a five to ten minute period of intense retching followed by the regurgitation of from 20 to 30 c c of a thick, tenacious, stringy mucus. This slimy material is the typical secretion of acute strangulation and it varies little, either in character or amount, from this point until death. Stercoraceous or fecal vomiting is never seen. This substantiates the belief that fecal vomiting never occurs in obstruction, but rather that the foul smelling fluid in low simple obstruction is due to the bacterial decomposition of the stagnant intestinal secretions accumulating in the proximal segment.

An analysis of this characteristic strangulation secretion, which begins within forty-five minutes after the obstruction is produced, reveals the following facts. Physically it is a clear, yellowish viscid fluid resembling egg albumin. Chemically it is mucin, a glycoprotein, secreted by the goblet cells of the intestinal mucosa. Titration tests for proteolytic and lypolytic enzyme action are practically always negative, thus indicating a complete absence of pancreatic juice and succus entericus. After the first vomitus of stomach contents the regurgitated fluid is always alkaline and gives a negative test for traces of free and combined hydrochloric acid. Gmelin's and Pettenkofer's tests for bile pigment are always negative. At necropsy the gallbladder is never distended and usually contains but little bile.

Kidney excretion shows a similar inhibition. Practically all dogs dying fifteen hours or less have an almost complete postobstructive anuria. Micturition does not occur and at necropsy the bladder is usually empty. The increase in blood urea and nonprotein nitrogen previously noted is evidently largely due to retention.

## SUMMARY

The entire picture then reveals the following facts

1 That in acute strangulation dehydration is an almost negligible factor, the total intestinal secretory loss being less than 200 or 300 c c  
Urinary secretion is almost nil

2 There is no appreciable loss of bile, pancreatic, intestinal, or gastric juices, but rather there is a total inhibition of these secretions

3 The absence of urine and the extreme fall in blood pressure indicate that the kidney and adrenals suffer in a like manner from this extreme systemic depression

4 The absence of hydrochloric acid in the vomitus plus the relatively normal blood chlorids and the absence of alkalosis rules out of consideration hypochloremia as a lethal factor

## COMMENT

A careful clinical comparison of patients with simple obstruction and acute strangulation shows that the two processes are radically different. The former lives from three to eight days without food or water, dying eventually either of (1) inanition and dehydration, or (2) peritonitis following perforation. Collapse symptoms are not present until the last day. The course is a slow, gradually progressive one which terminates fatally, in toxemia or collapse. On the other hand, strangulation is an acute affair characterized by profound collapse and resulting in death usually in less than thirty-six hours. In a previous paper we have shown that experimentally and clinically this classification is justified.

Acute strangulation has been further subdivided into (1) long loop obstruction and (2) short loop obstruction. Clinically, the first group is represented by volvulus, and extensive internal strangulation, the second by strangulated inguinal, femoral and umbilical hernias and intussusception. We have shown that in both of these groups the course is so rapid that hypochloremia, alkalosis, dehydration and inanition do not have time to develop. It is thus evident that the usually assumed causes of death in simple obstruction play little or no part in acute strangulation.

With long loops the predominant lethal factor is shock. This is indicated by the early and extreme fall in blood pressure, fast thready pulse, rapid sighing respirations, marked thirst, subnormal temperature, and pronounced muscular weakness. The rapid recovery following the release of the strangulation and the slight toxicity of early loop fluid further verifies this statement. The factors producing this shock are as follows: (1) excruciating pain due to the constant stretching of the visceral and parietal peritoneum by violent peristalsis and abdominal

distention, (2) low blood pressure and its direct effects, namely, diminished rate and volume of blood flow, capillary stasis, decreased metabolism, glandular inactivity, etc., (3) blood loss from hemorrhage into the bowel lumen

If the loops are short, shock, although present, is not of sufficient intensity to cause death. The dogs withstand this primary systemic depression and thus sufficient time is allowed for toxemia and peritonitis to develop. The poisonous products responsible for the development of this toxemia are not formed in the intestine above the obstruction but are produced by bacterial decomposition within the strangulated loop.

In brief, then, death in acute intestinal strangulation is due to a varying combination of shock and toxemia. The preponderance of one or the other of these causes being largely determined by the length of bowel involved and the degree of venous occlusion.

A point of considerable clinical interest is the fact that an intestine segment when strangulated always stretches two or three times its former length. For example, a loop 12 inches (30 cm) long at operation shows at necropsy a length of 30 inches (76 cm) or more. It is thus evident that the measurements given in surgical reports of gangrenous bowel resection do not represent the actual length of intestine involved.

#### CONCLUSIONS

1 Dehydration, hypochloremia, alkalosis and inanition are not present to any appreciable degree in acute intestinal strangulation.

2 The blood chemistry estimations show a considerable increase in urea and nonprotein nitrogen. The other constituents remain practically normal.

3 The length of the strangulated segment determines the degree of shock, toxemia and the rapidity with which death ensues.

4 The loop fluid of long segment strangulation is relatively nontoxic when injected intraperitoneally.

# THE DETERMINATION OF PHENOLSULPHONE- PHTHALEIN IN THE URINE IN JAUNDICE \*

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The purpose of this communication is (1) to discuss the errors introduced during the colorimetric determination of phenolsulphonephthalein in the urine when the color of the dye is obscured by the bile pigments, and (2) to offer a method which permits of fairly accurate estimation of renal function, as expressed by the rate of excretion of phenolsulphonephthalein even though marked jaundice is present

Rowntree and Geraghty <sup>1</sup> noted in their paper, in 1910, that urinary and biliary pigments may be removed from urine by basic lead acetate. No details of the use of this substance were discussed. In 1921 a method was reported by Burwell and Jones, <sup>2</sup> in which it was proposed that the use of a saturated alcoholic solution of zinc acetate precipitated both bile and blood pigments. The following paragraph is a quotation from the paper suggesting the use of zinc acetate

Phenolsulphonephthalein is injected in the usual manner, and the urine collected after the usual interval of two hours and ten minutes. This specimen is diluted up to 500 cc with tap water. To 20 cc of this diluted urine is added 20 cc of a saturated alcoholic solution of zinc acetate, which precipitates out bilirubin and hemoglobin. Filtration yields a clear solution, now free of bile pigments and hemoglobin. Twenty cubic centimeters of this clear filtrate is made alkaline with 5 cc of saturated sodium hydroxide solution to bring out the full color of the dye, and made up to 40 cc with tap water. This solution is clear and is read directly against a known standard of phenolsulphonephthalein. In order to correct for dilution, the percentage reading is multiplied by two.

In a preceding paragraph this statement is made "This procedure permits practically 100 per cent of phenolsulphonephthalein to remain in the filtrate." In the controls which were made by the authors who suggested the use of zinc acetate, no mention is made of the volume of jaundiced urine to which the estimated phenolsulphonephthalein had been added.

## I ERRORS INTRODUCED BY THE PRECIPITATION OF BILE PIGMENTS BY ALCOHOLIC ZINC ACETATE

When a known and constant quantity of phenolsulphonephthalein is added to increasing volumes of similar urine obtained by mixing

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\* From the Medical Department of Mount Sinai Hospital

1 Rowntree, L G, and Geraghty, J T J Pharmacol & Exper Therap  
1 579, 1909-1910

2 Burwell, C S, and Jones, C M The Removal of Bile and Blood from  
the Urine, J A M A 77 462 (Aug 6) 1921

numerous specimens from a deeply jaundiced patient, and the phenolsulphonephthalein determined by precipitation with zinc acetate following the methods described in the foregoing, two results have been obtained in the experiments of the author which do not agree with those reported previously

One 0.5 cc of phenolsulphonephthalein was added to varying volumes of urine from a patient suffering from obstructive jaundice. Determination with Hynson, Dunning and Westcott standards checked with known concentrations of dye. Six milligrams of dye per cubic centimeter when diluted to 1 liter equals 100 per cent. Bile pigments were precipitated by the zinc acetate method.<sup>2</sup>

TABLE 1—*Adsorption of Dye When Zinc Acetate Is Used*

Volume of Urine, Cc	Phenolsulphone-phthalein Added, per Cent	Phenolsulphone-phthalein Estimated, per Cent	Phenolsulphone-phthalein Loss, per Cent	Color Comparison
50	50	50	0	Excellent
100	50	45	10	Good
150	50	40	20	Fair
200	50	35	30	Poor
250	50	30	40	Poor

In a series run with a specimen of urine obtained from a case of partial obstruction of the common duct, the average loss, when 250 cc of urine was used with varying quantities of phenolsulphonephthalein, was less than 25 per cent and the colorimetric comparisons were good or fair throughout. The loss was negligible when similar experiments were done with normal urine. Comparing these figures with those in Table 1, it follows that with increasing concentration of bile pigment there is an increasing loss of phenolsulphonephthalein when the bile pigments are precipitated by alcoholic zinc acetate, and similarly the color comparison becomes less efficient. With urine containing less bile pigment, a better color comparison is obtained and there is less dye lost during precipitation. It should be noted that with the urine used in the experiments described in Table 1 the colorimetric comparison was poor when the urine volume was 200 cc. Above this more or less critical volume for that specimen of urine, comparison was unsatisfactory. Similar results have been obtained with other concentrations of dye which are encountered in this test of renal function, the critical volume dependent, of course, on the concentration of bile pigment.

From the foregoing it is evident that the determination of phenolsulphonephthalein in the presence of jaundice by the precipitation of bile pigments by alcoholic zinc acetate may lead to uncertain results because of the variable loss of the dye during the process of precipitation. The dye is probably adsorbed by the zinc pigment precipitate.

## II THE ADSORPTION OF PHENOLSULPHONEPHTHALEIN INCIDENTAL TO THE USE OF BARIUM HYDROXID AS A REAGENT TO PRECIPITATE BILE AND URINARY PIGMENTS

Another substance, barium hydroxid, has been used by the author to remove bile and urinary pigments from the urine where it was desired to determine phenolsulphonephthalein

Advantage was taken of the fact that bilirubin is believed to be an organic acid,<sup>3</sup> whose salts of the alkaline earth group of metals are insoluble in basic solutions. Barium,<sup>4</sup> one of that group, is particularly suitable, not only because it precipitates both bile and urinary pigments, but also because it forms a fairly concentrated solution of its hydroxid (about fifth molar), at ordinary temperatures. It is highly ionized, and hence there is available a high concentration of hydroxyl ion. From these properties it follows that if barium hydroxid is added in sufficient quantity to urine containing phenolsulphonephthalein, bile pigments and

TABLE 2—*Adsorption of Dye When Barium Hydroxid Is Used*

Volume of Urine, C c	Phenolsulphone-phthalein Added, per Cent	Phenolsulphone-phthalein Estimated, per Cent	Phenolsulphone-phthalein Loss, per Cent	Color Comparison
50	50	45	10	Excellent
100	50	40	20	Good
150	50	36	28	Good
200	50	30	40	Fair
250	50	25	50	Poor

urinary pigments, the pigments will be precipitated and the color of the dye brought out. After dilution and filtration, suitable colorimetric comparison is possible under most circumstances.

It has been shown previously that there is a loss of phenolsulphonephthalein during the precipitation of zinc pigment compounds. Does adsorption of dye also occur when barium hydroxid is used?

Table 2 illustrates that adsorption does take place. The urine was from the same collected specimen used in the experiments of Table 1. The procedure was as follows. After addition of dye and barium hydroxid, the mixture was diluted to 1 liter and filtered. It has been found that the amount in cubic centimeters of saturated barium hydroxid necessary to produce good colorimetric comparisons is equal to the volume of urine plus 50 c c, that is, with 50 c c of urine, 100 c c of barium hydroxid is used, in the same way with 100 c c of urine, 150 c c of barium hydroxid, has given the best determinations. Dilu-

3 Mathews, A. P. *Physiological Chemistry*, New York, William Wood & Co., 1916, p. 414-415.

4 Smith, A. *Inorganic Chemistry*, New York, Century Company, 1915, p. 331, 612.

tion of a portion of the filtrate with its own volume permits of better comparison with the standard and serves as a check

An excess of saturated barium hydroxid (equal to the volume of urine plus 50 c c ) is added to the urine volumes noted in Table 2. The addition of phenolsulphonephthalein and its determination is as in Table 1. Dilution to 2 liters permits better color comparison and readings.

Table 2 is apt to be misleading. Barium hydroxid does not always give colorimetric comparisons better than zinc acetate. Quite often the reverse is true. It is almost invariably so, however, when the urine contains much bile pigment. Under these circumstances, in the hands of the author, better colorimetric comparisons are available, if an excess of barium hydroxid is used. Because of this and because of the simplicity of the technic (only one reagent beside the phenol-sulphonephthalein is needed), the influence of barium hydroxid on urine containing bile pigments and phenolsulphonephthalein has been studied within the ranges of dye encountered in the performance of the phenol-sulphonephthalein test. From the results, a fairly accurate method of determination of the dye in jaundice has been developed.

### III THE RELATIONS BETWEEN THE QUANTITY OF PHENOL-SULPHONEPHTHALEIN PRESENT AND ITS ADSORPTION DURING BILE PIGMENT PRECIPITATION

In general, finely divided solids unite with substances in solution, so that if the solid be filtered off, the finely divided material previously in suspension contains more or less of the substance in solution. Adsorption<sup>5</sup> is the term generally used to describe this process of separation. There is somewhat of a direct relationship between the adsorbing surface and the adsorbed material. The amount adsorbed by charcoal, for example, at a given temperature is given by the expression  $\frac{X}{m} = K \frac{C}{C_1/n}$  where  $X/m$  is the amount adsorbed per unit weight of charcoal,  $C$  is the equilibrium concentration of the substance in solution, and  $n$  and  $K$  are constants determined empirically. The curve of the reaction drawn by plotting the amount of chemical change (quantity adsorbed) against the equilibrium concentration is a parabola. The more dilute the solution the greater is the quantity adsorbed, and at these dilutions the curve of adsorption is for practical purposes a straight line. This is especially significant in the adsorption of phenolsulphonephthalein by the barium precipitate for (1) the dilution is low, ranging from 0 mg to 6 mg (0 to 100 per cent), (2) the range is so small that theoretically a

5 Bechold, H. Die Kolloide in Biologie und Medizin, Dresden and Leipzig, Theodor Steinkopff, 1922, p. 21 et seq.



straight line of adsorption should be obtained with adsorption experiments over the concentration range of dye. If the adsorption curve is a straight line, then a method presents itself by which the error introduced by adsorption may be measured.

Table 3 shows some of the protocols of experiments performed to determine the relation between the concentration of the dye present and the quantity adsorbed. Barium hydroxid in excess was used on collective urines obtained from cases of jaundice of different severity.

The relation between dye added and subsequently adsorbed after addition of barium hydroxid. Within the limits of error of the experiments, for clinical purposes, the adsorption of phenolsulphonephthalein in the range studied is constant for a given specimen of urine containing bile pigment.

TABLE 3—*Protocols of Experiments*

No	Volume of Urine, C c	Phenol-sulphone-phthalein Added, C c <sup>3</sup>	Phenol-sulphone-phthalein Estimated, per Cent	Phenol-sulphone-phthalein Loss, per Cent	Color Comparison
1	150	0.1	5	50	Poor
	150	0.3	20	33	Fair
	150	0.5	35	30	Fair
	150	0.8	52	35	Fair
2	250	0.2	15	25	Good
	250	0.4	30	25	Good
	250	0.6	50 (?)	17 (?)	Good
	250	1.0	70	30	Good
3	150	0.20	15	20	Poor
	150	0.35	27	23	Fair
	150	0.50	40	20	Fair
	150	0.75	55	26	Fair
	150	1.00	80	20	Good

From Table 3 the following conclusions may be drawn:

(a) The quantity of adsorbed phenolsulphonephthalein in a given specimen of urine whose pigments have been precipitated by barium hydroxid is approximately a constant within certain limits of dye concentration.

(b) Given a jaundiced urine containing an unknown amount of phenolsulphonephthalein, after the determination of the dye, the quantity lost by adsorption may readily be estimated if to an aliquot portion of the phenolsulphonephthalein containing urine a known amount of dye

6 Occasionally from 0 per cent to 30 per cent of dye in other series gave figures which were not as close to the curve as those listed. Careful repetition of these revealed no discrepancy between the theoretical and experimental value except when extraneous pigment interfered or not enough barium hydroxid was used. With a concentration of the dye, say 25 per cent there is quite a difference in the percentage adsorption if the reading taken is 22 per cent or 18 per cent. The former gives a value of 12 per cent, the latter 28 per cent. It is obvious that such a close estimation cannot often be made, but yet it does not interfere with the value of the knowledge of the adsorption curve.

is added and the total dye then be determined similarly. The total should not be greater than 100 per cent. The percentage adsorbed then may be found as follows:  $x$  equals the percentage of phenolsulphonephthalein determined in specimen containing unknown quantity of dye,  $k$  equals the percentage of phenolsulphonephthalein added to aliquot portion,  $p$  equals the percentage of phenolsulphonephthalein determined in aliquot portion containing known plus unknown quantities,  $p - x$  equals the percentage of phenolsulphonephthalein of added known not adsorbed per unit mass of precipitate,  $\frac{p-x}{k}$  equals the fraction of  $k$  not adsorbed per unit mass of precipitate,  $\frac{\frac{p-x}{k}}{\frac{p-x}{k}} = \frac{kx}{p-x}$  equals  $x'$ , the final corrected reading for adsorption.

Theoretically, it may be expected that for similar microdeterminations of dyes where adsorption occurs, the correction for adsorption may be obtained in the same fashion.

(c) The greater the concentration of dye, the more accurate is the colorimetric comparison.

#### IV THE PHENOLSULPHONEPHTHALEIN TEST IN JAUNDICE

The method devised from the studies on adsorption differs from the routine as follows. When there is no correction for adsorption:

1. It is preferable to give the dye intravenously but intramuscular injection is almost as suitable.

2. Divide the two hour specimen into two equal parts.

3. To one part add an excess (urine volume plus 50 cc) of saturated barium hydroxid. Dilute to 500 cc or 1,000 cc. Filter. Compare a portion of the filtrate with standards. If the 500 cc dilution is used, the reading is direct. If 1,000 cc is the dilution, the two hour excretion is the reading  $\times 2$ . It is of course only necessary to catch a few cubic centimeters of the filtrate. The dilution to 2 liters aids in colorimetric comparison.

4. If the total two hour percentage of excretion of dye is normal or only 5 or 10 per cent below the lower limits of normal, the reading stands as the excretion of the dye and the excretion may be considered normal.

When correction for adsorption must be evaluated:

5. If the reading obtained is below normal, it must be determined whether the diminished excretion of the dye is actual or is due to adsorption. To the remaining half of the excreted urine, whose dye content has been determined, add 0.25 cc (for 500 cc dilution) or 0.50 cc (for 1,000 cc dilution) of phenolsulphonephthalein. With intense jaundice and large urine volume the latter is preferable. Redetermine, in this control, the percentage of dye.

6 The second reading in (5) minus the first in (4) gives the quantity of dye not adsorbed. For example, if the first reading (apparent two hour excretion) had been 20 per cent, and if to the remaining portions 0.25 c c of the dye had been added, the second reading, granting that none had been lost by adsorption, would be 20 per cent plus 50 per cent (0.25 c c dye to 500 c c) or 70 per cent. If the reading was 50 per cent instead of 70 per cent, it is evident that the added dye only gave an additional 50 per cent minus 20 per cent, or 30 per cent of color. Hence, three-fifths of the dye added was determined, and two-fifths lost by adsorption.

7 The final reading corrected of excreted dye is equal to the first reading divided by the fraction not adsorbed or following the foregoing example  $\frac{20\%}{3/5} = 20\% \times 5/3 = 33\%$

#### SUMMARY

1 The indiscriminate use of alcoholic zinc acetate or saturated barium hydroxid to remove bile pigments from urine containing phenol-sulphonephthalein in jaundice may give erroneous readings, because of adsorption of the dye.

2 A relatively more accurate method using saturated barium hydroxid as precipitant is described, in which the loss of dye by adsorption may be estimated.

# ADHESIONS IN THE UPPER RIGHT ABDOMEN

## A CLINICAL TEST COMPARED WITH THE ROENTGEN-RAY FINDINGS <sup>1</sup>

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PHILADELPHIA

In 1922 Lyon<sup>1</sup> described a new clinical test for determining the presence of adhesions in the upper right quadrant of the abdomen. This test is based on the transmission of the musical note of a tuning fork, placed in contact with the skin over the liver, to the bell of a stethoscope placed over the stomach. In his article Lyon stated that this method had been checked against roentgen-ray and operative findings, but he gave no statistics as to the result in a series of cases. It was this fact that prompted the present investigation.

In the present stage of the development of diagnostic procedures the roentgen ray, in competent hands, offers the most reliable method short of visual inspection, for the determination of adhesions in the upper right abdomen. It therefore seemed worth while to compare the new method with the old, keeping in mind, however, the possibility of error in the interpretation of the roentgen-ray study.

This test is described by Lyon as "an accurate clinical method of determining adhesions between the stomach and neighboring viscera, but particularly useful for the detection of adhesions between the pyloroduodenal segments and the under surface of the liver or other parts of the gall tract."

### THE TEST

The test is performed with the patient recumbent and the abdomen and lower thorax exposed. A tuning fork (a G fork of 410 vibrations was used) is struck gently against a solid object, and with the bell of the stethoscope over the stomach in the left hypochondrium, the lower border of the stomach is mapped out by applying the stem of the fork to the abdominal wall in the following manner. The stem should be applied firmly and at right angles to the surface of the abdomen and the note of the fork should not be too loud. Beginning below the level of the umbilicus at first the note heard through the stethoscope will be faint and distant, but as the fork is successively applied closer to the

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<sup>1</sup> From the Stomach Department, Jefferson Hospital

1 Lyon, B B V Surg, Gynec & Obst 35 232 (Aug) 1922

costal margin this note will abruptly change to a sharp clear tone when the stem of the fork is placed above the lower border of the stomach. This change has no relation to the proximity of the tuning fork to the stethoscope. Having in this way determined the true gastric note, the fork is then moved toward the right costal margin until this note is lost or the rib margin reached. The transmission is then tested through the liver by placing the stem of the fork above the right costal margin. In placing the stem of the fork on the abdomen, care must be taken that the skin is not put under tension between the fork and the bell of the stethoscope, or a sharp musical note will be transmitted superficially. In placing the bell of the stethoscope below the left costal margin the question of an underlying colon may be raised but this can be ruled out by placing the stethoscope above the costal margin and again determining the lower border of the stomach.

#### INTERPRETATION OF TEST

As to the interpretation of this test Lyon says

In normal cases one does not ever get the tuning fork note transmitted constantly through the liver to the bell of the stethoscope placed over the stomach.

In pathologic cases, however, I have learned to differentiate the following types

First, when the musical tuning fork note is transmitted from the left half of the right costal margin and this phenomenon is found to be constant at each examination, I would expect to find rather slight formation of adhesions between the pylorus or duodenum and the peritoneal coverings in the neighborhood of the gall ducts.

Second, when the note is transmitted from the costal margin in the region of the ninth and tenth ribs, but is not transmitted through the liver, I would expect to find at operation that the adhesions are more likely to involve the gallbladder.

Third, when the musical note is transmitted from the tuning fork along the length of the right costal margin from the epigastric border to the anterior axillary line, and is very clear and distinct and is always constant, I would expect to find rather older and denser adhesions attached to the looser neighborhood structures, gall ducts, gallbladder and gastrohepatic omentum.

Fourth, when the tuning fork note is constantly transmitted through the liver and heard above the right costal margin, I would expect to find adhesions between the pylorus or duodenum and the under surface of the liver. The clear distinctness of the transmitted note and its wider distribution over a larger area of the liver suggests that the adhesions are denser in character or more widespread. All these tuning fork transmissions of the gastric note will be enhanced if 3 or 4 ounces of air is injected into the stomach.

With all these minutiae of differential diagnosis I cannot agree, especially when unsupported by the definite evidence of a large series of cases, carefully studied at operation or at necropsy. In spite of this I do believe that the transmission of the tuning fork note from the stomach to the right costal margin is not found in normal cases, and is strong clinical evidence of adhesions in the upper right abdominal quadrant. Of course this test, like all other clinical procedures, is influenced

by the personal equation and differences in interpretation, but familiarity with the differences in transmission in normal and pathologic cases will prove a great aid in the study of the upper right abdomen

#### COMMENT

As to the rationale of this test, I believe that it is based on certain physical facts. When adhesions unite the pyloroduodenal segment to the under surface of the liver, or to other structures, such as the gall-bladder, which are in anatomic union with the liver, there is formed a continuity of anatomic structure between the liver and the walls of the stomach. If now the stem of the vibrating tuning fork is placed over the liver, the vibrations are transmitted directly from that organ to the walls of the stomach. The air bubble, which in the dorsal position lies in the left hypochondrium, acts as a resonator for the vibrations, amplifying them so that they can be heard by the overlying stethoscope. Mere apposition of structures does not produce the same sharp clear note, because the vibrations are dampened in passing from one structure to the other. An every day example of this is the toy telephone, consisting of two cylinders each closed at one end by a diaphragm and connected by a taut string. The voice is readily transmitted by the string, whereas if the cylinders were placed on each side of a wall no sound would be transmitted.

The patients forming the present series of cases were selected because they all had a complete gastro-intestinal roentgen-ray study. The tuning fork test was done in the course of the routine physical examination at the patient's first visit and the results recorded at that time. The roentgen-ray studies were made at a later date, usually within a week. It might be said here that the roentgenologist did not know that any comparison of his findings with another method was being made. Only the result of the first tuning fork test is recorded here so that there would not be the unconscious influence of a knowledge of the roentgen-ray findings. A total of fifty cases is reported.

In thirty-five of these cases the tuning fork test and the roentgen-ray findings agree (Table 1). In explanation of the large number of positive findings it might be said that these patients were studied in a gastro-intestinal clinic and only those in whom an organic lesion was suspected were roentgenogrammed. In six cases the tuning fork test was positive but the roentgen ray, while showing pathologic changes in the upper abdomen, did not definitely demonstrate adhesions in the right quadrant (Table 2). In these cases the presumption of adhesions is strong, as they all show evidence of inflammatory conditions in the upper abdomen, and therefore they are closely associated with the cases in the first group. In nine cases the tuning fork and the roentgen-ray findings did not agree (Table 3).

TABLE 1—*Cases in Which the Tuning Fork and Roentgen-Ray Findings Agree*

Case	Tuning Fork	Roentgen Ray Findings in Upper Abdomen
1	Positive	Periduodenal adhesions, partial obstruction
2	Positive	Adhesions causing definite deformity of duodenum
3	Positive	Second portion of duodenum constricted from ulcer or adhesions
4	Positive	Duodenum irregular, persistent cicatricial duodenal ulcer
5	Positive	Duodenum irregular, probable adhesions
6	Positive	Duodenal adhesions second portion
7	Positive	Adhesions to second portion of the duodenum
8	Positive	Organic obstructive lesion involving pylorus
9	Positive	Periduodenal adhesions
10	Positive	Periduodenal adhesions
11	Positive	Perihepatic adhesions
12	Positive	Duodenum irregular, possible periduodenal adhesions
13	Positive	Perigastric and periduodenal adhesions
14	Positive	Probable periduodenal adhesions or bands
15	Positive	Diverticulum second portion of duodenum, adhesions in upper right quadrant
16	Positive	Periduodenal adhesions
17	Positive	Probable periduodenal adhesions
18	Positive	Periduodenal adhesions with adhesions to the hepatic flexure
19	Positive	Periduodenal adhesions
20	Positive	Periduodenal adhesions
21	Positive	Periduodenal adhesions
22	Positive	Periduodenal adhesions
23	Positive	Periduodenal adhesions
24	Positive	Persistent deformity of the duodenal cap
25	Positive	Periduodenal adhesions
26	Positive	Periduodenal adhesions
27	Positive	Duodenum shows irregular filling due to ulcer
28	Positive	Periduodenal adhesions
29	Negative	Duodenum negative
30	Negative	Duodenum negative
31	Negative	Duodenum negative
32	Negative	Duodenum negative
33	Negative	Duodenum negative
34	Negative	Duodenum negative
35	Negative	Duodenum shows no filling defect or delay

TABLE 2—*Cases in Which There Is Roentgen-Ray Evidence of Pathology in the Upper Abdomen but No Involvement of Duodenum*

Case	Tuning Fork	Roentgen-Ray Findings
1	Positive	Probable prepyloric ulcer, duodenum negative
2	Positive	Duodenum flattened but not fixed
3	Positive	Probable cholecystitis, duodenum negative
4	Positive	Adhesions in upper left quadrant involving stomach and splenic flexure
5	Positive	Duodenitis? Gastric hypermotility
6	Positive	Small persistent mensura on the lesser curvature just prepyloric

TABLE 3—*Cases in Which the Tuning Fork and Roentgen-Ray Findings Do Not Agree*

Case	Tuning Fork	Roentgen Ray Findings
1	Positive	No evidence of gastro intestinal pathologic condition
2	Positive	No evidence of gastro intestinal pathologic condition
3	Positive	Chronic appendicitis duodenum negative
4	Positive	No gastro intestinal pathologic condition
5	Negative	Duodenal adhesions with evident constriction
6	Negative	Periduodenal adhesions with obstruction
7	Negative	Periduodenal adhesions
8	Negative	Adhesions probably between duodenum and gallbladder
9	Negative	Probable duodenal ulcer Filling irregular

TABLE 4—*Percentage of Cases*

Tuning Fork	Roentgen Ray	Cases	Per Cent
Positive	Positive	28	74
Positive	Probable	6	15
Positive	Negative	4	11
		<hr/>	<hr/>
		38	100
Negative	Negative	7	58
Negative	Positive	5	42
		<hr/>	<hr/>
		12	100

Grouping these findings a little differently (Table 4) it will be seen that a positive tuning fork test, interpreted as strong presumptive evidence of adhesions, was present in thirty-eight cases. In 74 per cent of these thirty-eight cases the roentgen-ray study demonstrated the presence of adhesions in the upper right quadrant. In an additional 15 per cent the roentgen ray showed an inflammatory condition in the upper abdomen. This makes a total of 89 per cent of those cases giving a positive tuning fork test in which the roentgen ray was able to demonstrate definite upper abdominal pathologic changes. In only 11 per cent of the cases was the positive tuning fork test not confirmed by the roentgen-ray study. Of the twelve cases with negative tuning fork test the roentgen-ray study was in agreement in 58 per cent.

It is realized that in presenting this study the number of cases is small, and that the wisdom of checking one clinical method against another of less than 100 per cent accuracy is questionable. Still, as all such tests are influenced by the personal equation, it seemed justifiable to give voice to an impression, and my experience with this test has led me to the belief that it is of material aid in the clinical study of the upper abdomen. It is also hoped that some investigator with the material will compare this test with the findings on visual inspection.

#### SUMMARY

1 A little used test for adhesions in the upper right abdomen is compared with the roentgen-ray findings.

2 A total of fifty unselected cases is reported.

3 A positive tuning fork test is found to be strong presumptive evidence of an inflammatory condition in the upper abdomen, with adhesions to the under surface of the liver, being in agreement with the roentgen-ray findings in 89 per cent of the cases.

4 A negative tuning fork test is not of so great value, as it was in agreement with the roentgen-ray findings in only 58 per cent of the cases.



# THE INFLUENCE OF DIFFERENT KINDS OF OIL, INTRODUCED INTO THE RECTUM, ON GASTRIC SECRETION \*

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AND

J H KELLOGG, M D

BATTLE CREEK, MICH

For many years in his clinical work one of us (K) noticed that different kinds of oil, when introduced into the rectum of a patient in the evening had a harmful effect on digestion the next day, with a lack of appetite, heavy stomach, coated tongue and other symptoms of gastric disorder. He concluded from this that gastric secretion is inhibited by such a use of oils. The experiments of Pawlow<sup>1</sup> and his pupils (Lobasoff,<sup>2</sup> Virshubsky,<sup>3</sup> Sokoloff<sup>4</sup> and others) have proved that oils are inhibitors of gastric secretion, and that the inhibition has its origin in the mucosa of the small intestine.

Kellogg<sup>5</sup> explained the mechanism of this inhibiting effect, in the patients observed by him, by the following fact, which had been noted and proved in this clinic by Case<sup>6</sup>. It was found that with the roentgen ray one could frequently observe rapid and numerous reverse movements of the contents of the rectum through the ileocecal valve up into the small intestine. Evidently this state is not infrequent in patients where this valve does not quite fulfil its function of preventing the contents of the rectum from going back. This observation is in full agreement with the suggestions of German authors (Grutzner,<sup>7</sup> Swiezynsky,<sup>8</sup> Reach,<sup>9</sup> Uffenheimer,<sup>10</sup> and Kast<sup>11</sup>) regarding the hitherto unexplained

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\* From the Pawlow Physiological Institute of the Battle Creek Sanitarium

1 Pawlow, I P. The Work of the Digestive Glands, London, Griffin & Co., Ltd, 1910

2 Lobasoff, I O. Dissertation, Petersburg, 1896

3 Virshubsky, A M. Dissertation, Petersburg, 1900

4 Sokoloff, A P. Dissertation, Petersburg, 1904

5 Kellogg, J H. Incompetency of Ileocecal Valve, M Rec June 21, 1913

6 Case, J T. X-Ray Studies of the Ileocecal Region and the Appendix, Am J Roentgenol 4 77-111, 1912

7 Grutzner, P. Zur Physiologie de Darmbewegung, Deutsch med Wchnschr 48 897, 1894

8 Swiezynsky, I. Nachprufung d Grutzner'schen Versuche uber das Schicksal von Rectalinjectionen an Menschen und Tieren

9 Reach, F. Ueber rucklaufige Fortbewegung von Darminhalt, Prag med Wchnschr 44 549, 1902

10 Uffenheimer, A. Weitere Studien uber d Durchlassigkeit d Magen-darmkanales fur Bacterien, Deutsch med Wchnschr 46 1851, 1904

11 Kast L. Rucklaufige Stromung in der Speiserohre als Erklarung der belebten Zunge, Berl klin Wchnschr 28 947, 1906

regurgitation of small particles (lycopodium, grains of starch, grains of different insoluble dyes, etc) and of microbes (*B prodigiosus*) from the rectum up into the small intestine, and even up to the stomach and the mouth

Although these conclusions, and especially the methods by which they were reached, were severely, and not without reason, criticized by various authors (Christomanos,<sup>12</sup> Platenga<sup>13</sup>), still they deserve serious attention, the more so because the phenomena of the reverse movement of the contents of the intestines, both at the lower end of the small intestine and at its beginning, are firmly established.

Because of the clinical importance and the physiologic interest of the before-mentioned observations, Kellogg suggested that this question should be investigated experimentally. The investigation was carried on in the sanitarium

First of all it was necessary to find out which oils and in what degree have an inhibiting effect on digestion in the stomach when introduced into the rectum. Then it was necessary to seek for the source of this inhibition, i e., does the inhibiting reflex start from the rectum, from the end of the small intestine, or from both places?

The experiments of Boldyreff,<sup>14</sup> Pfluger,<sup>15</sup> Popelsky,<sup>16</sup> Studsinsky<sup>17</sup> and others have proved that in oils the active principle with respect to the secretory and the motor activity of the digestive tract are fatty acids. Therefore the oils most rich in these acids and most capable of being split with the formation of these acids are, when introduced into the rectum, the strongest inhibitors of digestion in the stomach. To be sure, this fact has only a theoretic significance because, first, the commercial oils used in clinics and laboratories always contain free fatty acids, and, second, even if the oils used are neutral when introduced in the stomach or the duodenum they soon begin to split, forming fatty acids because of the action of the traces of ferments always found on the mucosa of the digestive tract.

In order to obtain conclusive results, it was decided to conduct experiments on a number of dogs, and to investigate the inhibiting effect of oils both on the psychical side of digestion (appetite and the first phase of digestion) and on the chemical (second phase of digestion).

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12 Christomanos quoted by Swiczynsky

13 Platenga quoted by Reach

14 Boldyreff, W N. Der Uebertritt des natürlichen Gemisches aus Pankreassaft, Darmsaft und Galle in den Magen, Arch f d ges Physiol **121** 13, 1907

15 Pfluger, E. Arch f d ges Physiol **90**·1, 1902

16 Popelsky, L. Dissertation, St Petersburg, 1896

17 Studsinsky. Rusk Vrach, 1911, Nos 1, 2 and 3

The experiments were conducted on dogs with gastric fistulas and with esophagotomy

In the first series of experiments, the secretion of gastric juice was caused by merely showing tasty food (meat, bologna, etc.), to the dog, in the second series by means of "sham" feeding. After the normal quantity of secretion was determined and the qualities of the juice, acidity (hydrochloric acid) and pepsin contents (after Mett), were tested, the experiments with oils were begun.

Different oils were used in quantities ranging from 50 to 100 gm., the oils were introduced into the rectum at various time intervals (five,

TABLE 1—*Influence of Oils on Gastric Secretion Excitation by Showing Meat*

1 Norm				2 Oil Experiment			
Experiment No 31 1923 Dog No 4 Fed 18 hours previously, stomach empty, reaction alkaline				Experiment No 30 1923 Dog No 4 Fed 18 hours previously 300 gm boiled meat and about 600 c c oatmeal gruel 10 hours previously 100 c c cod liver oil introduced in rectum, stomach almost empty (less than 5 c c food), reaction acid			
Minutes		Juice, C c		Minutes		Juice, C c	
0 - 5		0 0		0 - 5		3 5	
5 - 10		0 0		5 - 10		0 9	
				10 - 15		0 6	
				15 - 20		0 6	
				20 - 25		0 4	
				25 - 30		0 5	
Excitation Started				Reaction Alkaline, Excitation Started			
0 - 5		2 0		0 - 5		0 0	
5 - 10		6 0		5 - 10		2 0	
10 - 15		9 0		10 - 15		4 0	
15 - 20		7 5		15 - 20		2 5	
		<hr/> 24 5				<hr/> 8 5	
Excitation Stopped				Excitation Stopped			
20 - 25		5 0		20 - 25		3 0	
25 - 30		2 5		25 - 30		2 0	
30 - 35		2 5		30 - 35		1 5	
35 - 40		0 0		35 - 40		0 5	
Acidity of juice collected during excitation				Acidity of juice collected during excitation			
Mett's test of the same juice				Mett's test of the same juice			
		0 30 per cent				0 28 per cent	
		0 09 inches				0 08 inches	

six and ten hours) before the experiments. The following oils were tested: mineral oils (liquid paraffin), vegetable oils (olive and linseed), and animal oils (butter and cod liver oil).

In general, the oils introduced into the rectum had a strong inhibiting effect on the quantity of gastric juice secreted, decreasing the secretion to one-half or one-third, normal, but they did not change the acidity or the pepsin content of the juice. Thus we see a difference between the inhibiting action of oil introduced into the rectum and that introduced into the stomach. In the latter case it decreases also the acidity and the pepsin content of the juice.

TABLE 2—*Influence of Oils on Gastric Secretion Excitation by Sham Feeding*

1 Norm				2 Oil Experiment			
Experiment No 4 July 16, 1923 Dog No 8 Weight of dog, 16,500 gm Fed 13 hours previously (500 gm meat), stomach empty, reaction acid				Experiment No 22 Aug 10, 1923 Dog No 8 Weight of dog 18,100 gm Fed 13 hours previously 500 gm meat and 100 gm bread, stomach empty, reaction acid 11 hours previously 100 c c olive oil introduced into rectum and remained there			
Minutes		Juice, C c		Minutes		Juice, C c	
0 - 5		2 8		0 - 5		0 0	
5 - 10		3 2		5 - 10		0 0	
10 - 15		2 6		10 - 15		0 0	
15 - 20		2 5		15 - 30		0 0	
20 - 25		2 6					
25 - 30		2 1					
Sham Feeding Started				Sham Feeding Started			
0 - 5		5 4		0 - 5		2 6	
5 - 10		21 7		5 - 10		11 0	
10 - 15		27 5		10 - 15		8 2	
15 - 20		23 1		15 - 20		2 1	
20 - 25		20 3		20 - 25		4 4	
25 - 30		18 0		25 - 30		5 1	
		<hr/> 116 0				<hr/> 38 4	
Sham Feeding Stopped				Sham Feeding Stopped			
Acidity of juice collected during sham feeding		0 54 per cent		Acidity of juice collected during sham feeding		0 46 per cent	
Mett's test of same juice		0 09 inches		Mett's test of same juice		0 10 inches	

TABLE 3—*Influence of Different Oils, Introduced into the Rectum, on The Gastric Secretion Excitation by Showing Meat\**

Date of Experiment, 1923	Juice, C c	Acidity, per Cent	Pepsin (after Mett)	Norm or Kind of Oil	Dog Number
April 30	40 0	0 30	0 08	Norm	25
June 10	25 6	0 24	0 11	Norm	25
June 29	16 0	0 31	0 08	Norm	4
July 2	22 0	0 23	0 10	Norm	9
July 18	24 5	0 30	0 09	Norm	4
September 6	18 5	0 20	0 09	Norm	6
May 6	1 4			Olive oil	25
August 6	3 9	0 22	0 11	Olive oil	9
August 13	10 1	0 24	0 11	Olive oil	9
May 3	17 8	0 29	0 07	Linseed oil	25
May 14	16 0	0 23	0 06	Linseed oil	25
July 12	8 5	0 28	0 08	Cod liver oil	4
May 8	47 5	0 52	0 10	Butter	25
May 6	43 6	0 40	0 09	Paraffin oil	25
May 16	25 5	0 28	0 09	Paraffin oil	25

\* Juice in each case was collected for twenty minutes

TABLE 4—*Influence of Oils on Gastric Secretion Sham Feeding\**

Date of Experiment, 1923	Juice, C c	Acidity, per Cent	Pepsin, (after Mett)	Norm or Kind of Oil
July 16	116 0	0 54	0 09	Norm
August 8	92 4	0 48	0 09	Paraffin oil
August 10	33 4	0 46	0 10	Olive oil
August 13	47 7	0 44	0 12	Cod liver oil
August 17	68 7	0 43	0 10	Linseed oil
August 20	103 6	0 50	0 14	Norm

\* Juice in each case was collected for thirty minutes

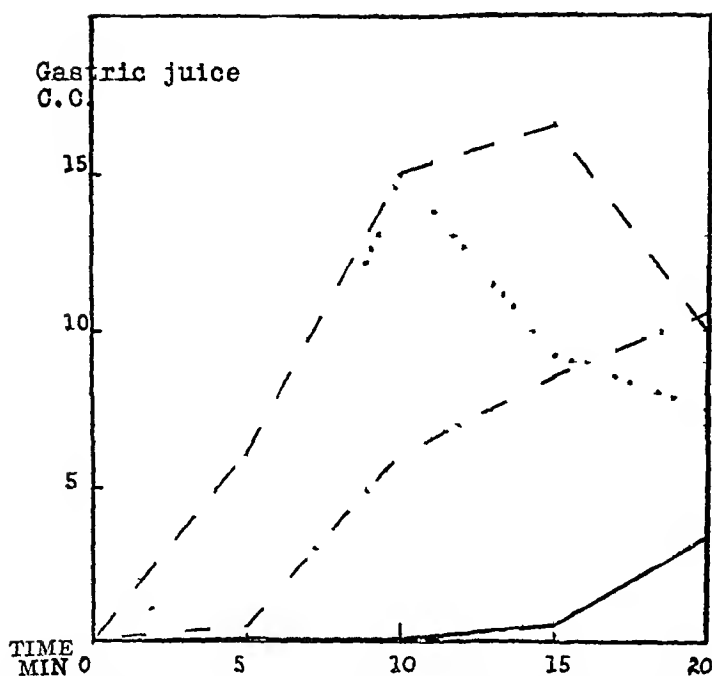


Chart 1—Influence of oils on gastric secretion Straight line, olive oil, broken line, butter, dot and dash, paraffin oil, dots, norm (average of three experiments)

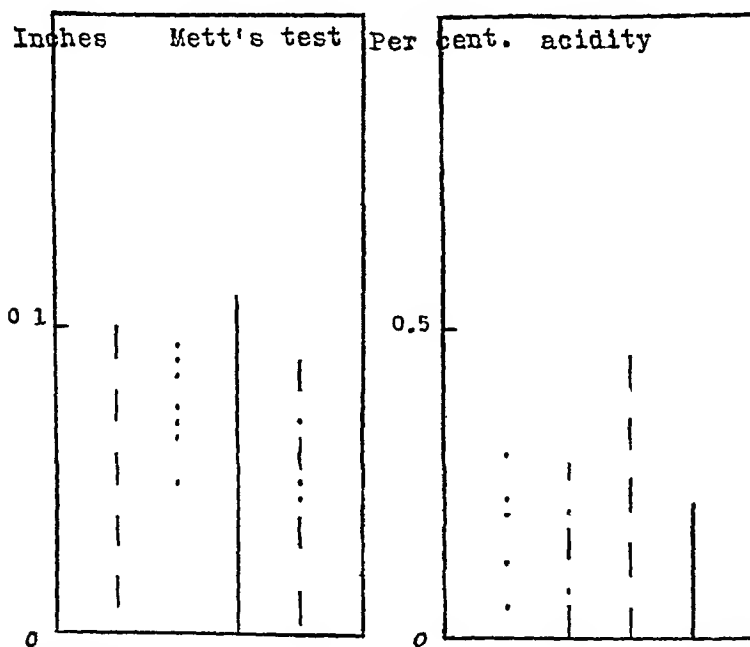


Chart 2—Excitation by showing meat The juice was collected for twenty minutes in each case

This inhibition is observed in cases of "appetite secretion" as well as in the case of "sham" feeding secretion of gastric juice

Altogether forty experiments were conducted on dogs, the results of which are given in the tables and charts

The mineral oil did not have any inhibiting effect, nor did the butter cause any inhibition, presumably because it is not liquid at body temperature, but is a viscous, thick mass which cannot move from the

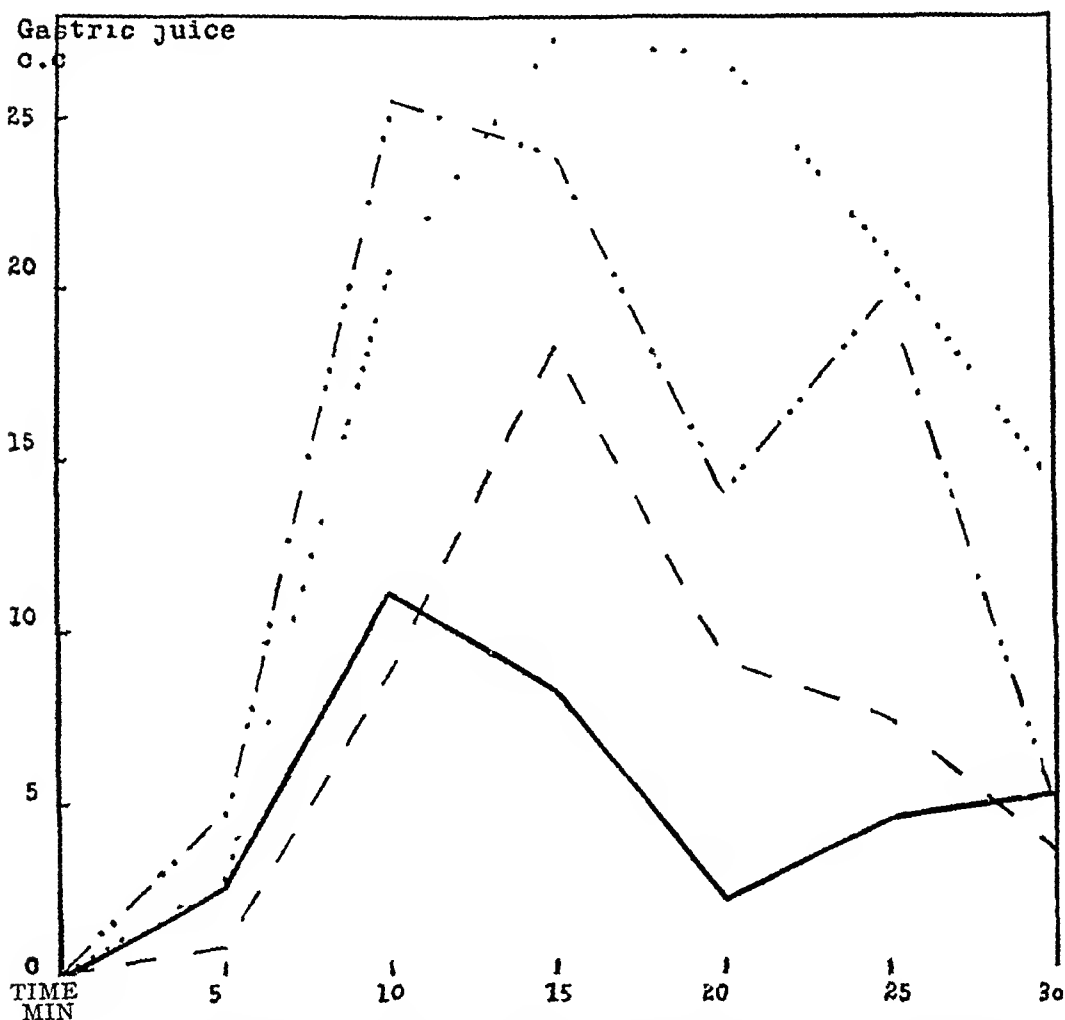


Chart 3—Influence of oils on gastric secretion in Dog 8 Straight line, olive oil, broken line, cod liver oil, dot and dash, paraffin oil, dots, norm (average of two experiments)

rectum into the small intestine and therefore cannot develop its inhibitory action

After the introduction of the oil, each dog was placed alone in a room with a smooth floor, and careful observation was made as to whether the oil remained in the rectum until the time of experimentation. If even a small part of oil escaped, the experiment was not conducted at all. In this way it was found that the active dose of oil is a quantity ranging from 50 to 100 c c

The works of Heidenham,<sup>18</sup> Pawlow,<sup>1</sup> Boldyreff<sup>19</sup> and others have proved that the acidity of the gastric juice as secreted from the glands of the stomach is always constant, the variations in its acidity, especially when the quantity of gastric juice is small (Tables 1 and 3), depend on different alkaline admixtures, added either from the stomach itself (gastric mucus) or from the duodenum (pancreatic juice and other intestinal juices)

Cod liver oil was found to produce a less strong inhibition, evidently because during its use it was almost impossible to get rid of its strong fishy odor, and the products made from fish, as has been shown by experiments of Boldyreff,<sup>20</sup> cause an abundant secretion of gastric juice

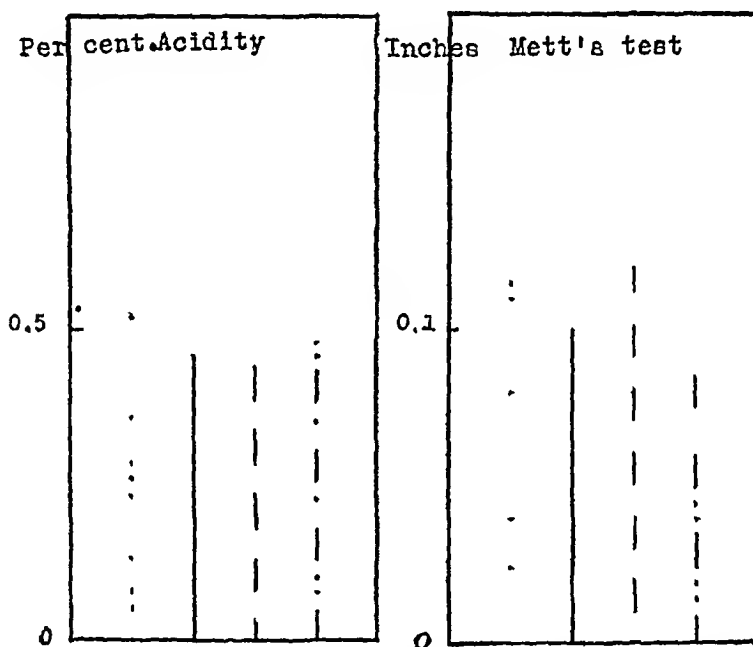


Chart 4—Sham feeding The juice was collected for thirty minutes in each case

#### EXPERIMENTS WITH NEUTRALIZED OIL

Occasionally experiments were carried out on a dog with a catarrhal affection of the stomach, in conditions somewhat pathologic and therefore corresponding to those of hospital or clinic observation. Results were the same.

The inhibition of gastric secretion by neutral oils begins after a longer period of time after the introduction of oil into the rectum than in case of commercial oils, containing free fatty acids.

The results obtained show that great care should be taken in the oil treatment of patients with certain kinds of stomach disorder.

<sup>18</sup> Heidenham, R. quoted by Pawlow

<sup>19</sup> Boldyreff, W. N. Quart J Exper Physiol 7 1-12, 1915

<sup>20</sup> Boldyreff, W. N. Boas' Arch 15 1, 268, 1909

TABLE 5—*Inhibiting Action of Neutral Olive Oil as Gastric Secretion Sham Feeding\**

Date of Experiment 1923	Kind	Juice, Cc	Acidity, per Cent	Pepsin (after Mett)	Remarks
August 10	Mean normal	111.7	0.49	0.10	Control
	100 c.c. olive oil (not neutralized) introduced in rectum 11 hours before experiment	33.4	0.45	0.10	Inhibition
September 28	100 c.c. neutral olive oil introduced in rectum 12 hours before experiment	121.3	0.49		No inhibition
October 1		61.3	0.48		Inhibition
November 16	100 c.c. neutral olive oil introduced in rectum 12 hours before experiment	106.1	0.5	0.10	Slight inhibition
November 21	100 c.c. neutral olive oil introduced in rectum 11 hours before experiment	109.7	0.4	0.09	Almost no inhibition
November 22		49.6	0.5	0.10	Inhibition

\* Juice in each case was collected for thirty minutes

TABLE 6—*Influence of Olive Oil Clysters on Weight of a Sick Dog*

Date	Weight, Gm	
September 28	17,800	Neutral oil introduced
September 29	17,600	
October 2	17,400	
October 4	17,000	
October 5	17,200	Neutral oil introduced
October 7	17,400	
October 19	17,800	
October 23	17,600	
October 30	17,900	
November 7	18,100	
November 16	18,100	Neutral oil introduced
November 17	17,900	
November 18	17,600	Neutral oil introduced
November 19	17,500	
November 21	17,500	
November 22	17,500	
November 23	17,200	
November 24	17,400	
November 30	17,500	
December 9	17,600	



## SUMMARY

The action of oils introduced into the rectum

1 The mineral oils (liquid paraffin oil) do not diminish the appetite, and do not have any harmful effect on gastric digestion

2 Of the animal oils, butter has no inhibiting action on digestion because it is not liquid at body temperature, and therefore cannot move into the small intestine Cod liver oil inhibits digestion, but in a relatively small degree

3 The vegetable oils (olive oil and linseed oil) inhibit very strongly the psychical phase of digestion

4 The fatty acids are the active substance in the oils

5 Commercial oils have a stronger inhibitory action, as they contain free fatty acids, but neutral oil also possesses this action, though in a less degree Moreover, the action of neutral oil is slower

6 The inhibiting action of oils introduced into the rectum consists only in decreasing the quantity of gastric juice, its acidity and pepsin content remain nearly constant

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## CORRECTIONS

In the September issue of the ARCHIVES OF INTERNAL MEDICINE, an error occurred in listing "Henry P Walcott, M D" as one of the authors of the article, "The Effect of Iodin in Exophthalmic Goiter" The authors of this article are

PAUL STARR, M D

Henry P Walcott Fellow, Harvard Medical School

HAROLD N SEGALL, M D

AND

JAMES H MEANS, M D

BOSTON

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In the article by Drs Brown and Coffey, published in the October issue, the centerhead, "Cases in which our method was used by others," which precedes the report of Case 9, page 437, should precede the report of Case 10, page 440

# Book Reviews

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CHARLES WHITE AND THE ARREST OF PUERPERAL FEVER J GEORGE ADAMI,  
CBE, MD, FRS, Vice-Chancellor of the University of Liverpool  
London, Hodder and Stoughton, Ltd, Price, \$5 00

This work contains the inaugural Lloyd Roberts Lecture delivered by the author before the Manchester Royal Infirmary, and an exhaustive collation of the writings of Charles White on puerperal fever

The lecture is a plea for just recognition of the work of Charles White and his English contemporaries in the prevention of puerperal fever, years before Semmelweis published his "Aetologie"

Indeed, Dr Adami demonstrates that White's "Treatise on the Management of Pregnant and Lying-In Women," published in 1773, demanded practically all the prophylactic measures insisted on by Semmelweis eighty years later, and that in 1826-1833 Collins, master of the Rotunda, was able to reduce the hitherto appalling mortality from puerperal fever at that institution to a minimum by the use of chlorinated lime and general adherence to the recommendations of White

Five editions of White's treatise were published during the twenty years succeeding its initial publication, translations appearing in both German and French

Of more than passing interest today is White's insistence on the importance of his patients sitting up as early as the second or third day, and its relation to womb drainage and foul and retained lochia

PALEOPATHOLOGY, AN INTRODUCTION TO THE STUDY OF ANCIENT EVIDENCES OF  
DISEASE By ROY L MOODIE, PH D, Associate Professor of Anatomy in  
the University of Illinois University of Illinois Press, Urbana, Illinois,  
1923

The word Introduction is unduly modest Dr Moodie, whose competency has been well demonstrated for a number of years by published articles and demonstrations of original material, has really made an encyclopedic study of an important topic never heretofore handled in the same way He has followed the geologic record down to about 600 B C in the old world and to the late pre-Columbian period in America, and, as he says (Preface) "These studies may be regarded as a synthesis of medical history, paleontology and anthropology" His hope "that the details of ancient pathologic lesions may aid in an understanding of the nature of disease" is reasonable, though its fulfillment depends on the broadness of view of students The absorbing question of the acquisition of some human diseases from animals in the early ages and the extinction of great groups of animals are some of the problems of paleopathology As this word was first defined less than thirty years ago it is not strange that so little is known None of the diseases so far discovered is likely to have directly endangered the life of the individual or the race As Dr Moodie says "Most of the ancient diseases may be regarded as chronic, infectious or constitutional" But evidences of some disease are present in all geologic periods While an immense fund of knowledge has been assembled by the author he justly says that he has not attempted many generalizations In rare cases the statements may seem hardly warranted as, in speaking (page 30) of the apparent immunity of early paleozoic animals to infectious diseases Considering

relatively small proportion of persons and species studied, it seems venturesome to assume that these organisms were free from disease. Equally venturesome seems the statement (page 38) that disease is relatively recent in its origin, and has afflicted the inhabitants of the earth for only the last quarter of its history, or twenty-five million out of a hundred million years. Is it not more likely that from the beginning disease was a close follower on life? But views that excite serious protest are rarely obtruded, and in general the author has observed a wise though critical and objective method of presentation. A brief synopsis of the contents will furnish some idea of the scope and value of the work. The Introduction gives a general sketch of the data, with a table showing the geologic periods and pathologic evidences. Chapter 1 describes the development of paleopathology with an account of the measurement of geologic time. In Chapter 2, on the Origin of Disease, a more detailed table of all geologic evidences of disease is presented. Chapter 3, on Pathological Conditions Among Fossil Plants, is contributed by Dr. Edward W. Berry of Johns Hopkins University, who gives a good account of that important subject. In Chapters 4 and 5, Callus and Fracture in Fossil Vertebrates are very fully illustrated and well described, as are also Deforming Arthritides in the Early Vertebrates. Chapter 6, on Caries and Alveolar Osteitis Among Fossil Vertebrates, may surprise those who look on dental caries as an affliction of high civilization and found only in *homo sapiens*. It may be added that in the Pleistocene fossilized human skeleton recently found in California, and supposed to be twenty-five thousand years old, absorption of the alveolar process and also osteophytes on the vertebrae are evident. Chronic Infections Among Fossil Vertebrates, Parasitism Among Fossil Animals, the Bacteriology of Past Geological Ages, Opisthotonos and Allied Phenomena furnish several more chapters. A short but very interesting chapter considers the Extinction of Races. This is followed by the Pathology of the Early Human Races, beginning with a description of the exostoses on the femur of *Pithecanthropos*, and including some remarks on Evidences of Syphilis Among Ancient Men and on Prehistoric Trephining, the Use of the Cautery, and amputations of fingers among primitive races. A more detailed discussion of syphilis would be welcome. The author may be correct in his belief that the tubercle of Carabelli (page 354) does not prove the existence of syphilis, but he seems to be at variance with many syphilographers when he states briefly that Hutchinson's teeth "have been recently shown to be due to faulty nutrition." Genuine and pseudo-Hutchinsonism seem to be confused. Chapter 13 on diseases of the Ancient Egyptians very properly begins with a biographical sketch of Sir Marc Armand Ruffer. The details are too numerous even to enumerate and of absorbing interest. Chapter 14 describes Diseases Among the Pre-Columbian Indians of North America and contains a discussion of the antiquity of American Indians. The final chapter describes Diseases of the Ancient Peruvians with accounts of some interesting types, such as gundu, verruga, still widespread, uta or leishmaniasis, and negua, due to the sand flea or jigger. Prehistoric trephining is here well described and richly illustrated, as are also diseases of the teeth. A very full bibliography and an excellent index add much to the usefulness of the book to students. An excellent feature and one that might well be imitated in many other scientific books is furnished by the biographic notices of authors cited. In many cases there are portraits. The illustrations on 117 plates are very numerous and in general are well produced and illustrate many things of interest besides pathologic changes, such as arrow heads in the tissues, trephining and other prehistoric scenes. The text as a rule is clear and lively but some expressions seem questionable, such as the frequent use of "pathology," "this pathology," for disease, lesions, or alteration. "Sir Ruffer" may be proper usage in revised court circles but in pre-war days would have been incorrect. The University of Illinois Press is to be congratulated on the high quality of

the mechanical execution of the book. No doubt the compositor and proof reader are responsible for the periods after the initials of W J McGee. The well known foible of one of the most interesting and most lovable of American anthropologists need hardly be disturbed. The work is a valuable addition to the literatures of both geology and pathology and as such must appeal to a very wide circle.

CLINICAL ASPECTS OF THE ELECTROCARDIOGRAM, A MANUAL FOR PHYSICIANS AND STUDENTS. By HAROLD E B PARDUE, M.D. Price \$4.00, pp 236, 56 illustrations. New York, Paul B Hoeber, 1924.

This book contains ten chapters, eight of which are devoted to the consideration of the normal and various types of pathologic electrocardiograms. In the former, variations in the curves from normal persons are pointed out, and in the latter the clinical significance of the pathologic variations is discussed. The ninth chapter deals with the theory of electrocardiograms, and the final chapter is devoted to the description and the operation of the Hindle electrocardiograph.

The author has endeavored to give a general summary of the current knowledge of electrocardiology, referring only to those experimental observations which have a direct bearing on the clinical interpretations of the pathologic electrocardiograms. A portion of the chapter on the theory of electrocardiograms is very technical, and it is questionable whether so much space should be devoted to this particular phase of the field in a book of this type.

The chapter on the description of the operation of the Hindle electrocardiograph is especially valuable to the beginner in this field. Instructions as to the operation of the instrument are given in a straightforward manner. The various difficulties that may be encountered are considered and the means of correcting them suggested. In general, the book covers a field, from the standpoint of which it was written, in a credible manner and is recommended to the profession.

HUMAN PROTOZOOLOGY. By ROBERT W HEGNER, PH.D., Professor of Protozoology, and WILLIAM H TALIAFERRO, PH.D., Associate Professor of Protozoology in the School of Hygiene and Public Health of the Johns Hopkins University. New York, The Macmillan Company, 1924.

"This book represents essentially the subject matter of the course in protozoology given by the writers in the School of Hygiene and Public Health of the Johns Hopkins University." The hope that it may be useful to students in other institutions and to health officers and physicians, expressed by the writers, seems certain to be realized, for they have made a noteworthy contribution to the subject and one for which there has been a decided need. From the enormous literature on the protozoa they have made a rigid selection, but have omitted nothing that a rather critical search has suggested. While human parasites give the leading motive, many allied forms in lower animals are mentioned and described so fully that the reader cannot fail to keep in mind the broader aspects of protozoology. The plan is to describe "the general biology of the protozoa, as indicated by each group studied, to give typical life histories of representative species, either from man or lower animals, and then to present a more detailed account of the species living in man." While the plan makes it an ideal text book for beginners, the more advanced worker will find it a very convenient reference work, and it should appeal especially to laboratory technicians who are obliged to deal so frequently with problems of pro-

tozoology A carefully selected bibliography of fifty-two pages and adequate indexes facilitate reference Wide knowledge of the literature is obvious on all topics The authors have wisely omitted the minute details of classification that so often needlessly consume the time of the clinical investigator The chapter on Diagnosis of Intestinal Protozoa is a model of straightforward information The illustrations, print and paper are unusually good Mistakes that enter so easily into the first edition of a work containing so many details are rare and comparatively unimportant A wide use is to be predicted for this work

## THE PATHOLOGY OF PNEUMONIA CAUSED BY BACILLUS INFLUENZAE DURING AN INTER- EPIDEMIC PERIOD\*

DORSEY BRANNAN, M D

AND

ERNEST W GOODPASTURE, M D

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The frequent association of *Bacillus influenzae* with the respiratory discharges and with the pneumonias which accompanied the pandemic of influenza, in 1918, gave an apparently reasonable foundation to the hypothesis that this bacillus was the etiologic agent of the initial disease. This assumption seemed at first the more acceptable in view of Pfeiffer's<sup>1</sup> discovery of the influenza bacillus in association with influenza during recurrences of the previous epidemic of 1889-1890, and his pronouncement that it was the cause of the disease.

Bacteriologic and pathologic studies made during and after the last outbreak however make it very doubtful that the influenza bacillus was more than a secondary invader associated with an as yet unknown virus of influenza.

It was soon found that while *Bacillus influenzae* was frequently a contributing cause of the pneumonia present in fatal cases, this bacillus was by no means universally in evidence, and there seemed to be a regional variation in the type of micro-organism predominating in the lungs, although the initial disease remained quite uniform. There was also conspicuous failure of experiments in attempting to transmit influenza to human beings and to animals by means of the bacillus of Pfeiffer, and to protect persons by prophylactic inoculation with vaccines prepared with it.

Numerous studies of the pathologic anatomy of influenza necessarily limited to patients dying of pneumonia, have not established a sufficiently constant relation of *Bacillus influenzae* to the pneumonic inflammation nor to any particular lesion, to add much of favorable evidence for its etiologic relation to the primary disease.

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\* From the William H. Singer Memorial Research Laboratory, Allegheny General Hospital.

<sup>1</sup> Pfeiffer, R. Ztschr. f. Hyg. u. Infektionskrankh. **13** 3, 1893.

Very characteristic changes have been demonstrated in the lungs of influenzal pneumonia in early stages, consisting essentially of a dilatation of alveolar ducts, a serous exudate and a deposit of hyaline material in the form of a membrane on the walls of the ducts and neighboring alveoli. These changes have been regarded as the result of an unknown virus of epidemic influenza, and as independent of secondary invading micro-organisms. This lesion has been demonstrated in influenzal lungs with and without an associated infection by Pfeiffer's bacillus.

It has, however, been definitely established that *Bacillus influenzae* did frequently produce a characteristic type of pneumonia. This consisted of a purulent bronchitis and bronchiolitis, usually with ulceration of the mucous membrane, dilatation of the affected air channels, an inflammatory exudate within their walls, a deposition of fibrin in alveoli immediately surrounding them, and a polymorphonuclear cell exudate in the terminal alveoli with little fibrin. In gross, the bronchioles were conspicuous on the cut surface as small gray or yellowish dots, a few millimeters in diameter, with a drop of pus in the center. This type of pneumonia was quite similar to that described originally by Pfeiffer as characteristically resulting from pulmonary infection with the influenza bacillus, and has apparently its only analogy in the interstitial bronchopneumonia due to a hemolytic streptococcus following measles, described by MacCallum<sup>2</sup> in his study of the pathology of the pneumonias in the United States army camps during the winter of 1917-1918. The pneumonia produced by the influenza bacillus ordinarily can be distinguished from this type by the frequent association of empyema and atelectasis of the lung with the latter.

It has been of interest, in view of these facts, to study the pathologic anatomy of five recent cases of acute bronchopneumonia in which the influenza bacillus was the predominant or an important infecting agent in the lungs. The occurrence of several instances of influenza bacillus pneumonia in adults in an interepidemic period within so brief a time is apparently unique. There was no indication of a local epidemic of influenza in Pittsburgh during this time. Burns of the Bureau of Infectious Diseases has kindly informed us that his mortality statistics show considerably fewer deaths during January and February of the present year (1924), the months during which these cases were observed, as compared with the same period in 1923. It is impossible to determine whether there was, at this time, an increase in the number of acute respiratory infections of a milder type which might have been caused by the influenza bacillus.

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2 MacCallum W. G. Monograph of the Rockefeller Institute for Medical Research, No. 10, 1919, Reports Johns Hopkins Hosp. 20:149 (Part II) 1921.

During January and February, 1923, of the 1,000 patients admitted to the Allegheny General Hospital, there were fifty-four cases of pneumonia of all kinds, and twenty-four deaths from this cause. For the same period, this year, of the 1,033 admissions, there were thirty-one cases of pneumonia, and seventeen deaths. It must be assumed, we believe, that an unusually virulent strain of *Bacillus influenzae* was active at this time and was responsible for the type of pneumonia which is to be described, a strain equally as virulent presumably as that which was associated with the past pandemic, in view of the fact that the pneumonia it produced was as extensive and as severe as that encountered in 1918. Yet in none of these cases was there an initial infection with so profound a toxemia as characteristically preceded the pneumonias of the great epidemic, and no evidence of a concurrent epidemic disease.

#### CLASSIFICATION OF CASES

In four of the five cases, the invasion by the influenza bacillus was associated with a pneumococcus infection. In two of these there was an onset characteristic of lobar pneumonia and at necropsy one or more lobes were involved by a more or less diffuse pneumonia containing pneumococci, but atypical in their gross pathologic anatomy, while other lobes presented lesions recognized grossly as caused by the influenza bacillus. A third case gave a history such as might have been due to primary influenza bacillus infection and the pulmonary lesions were caused by this organism alone, while a patch of fibrinopurulent pleuritis over one lobe was the result of a pneumococcus. The fourth case was that of an old man who had been on a drunken spree for several days. He had a blood stream infection with Type III pneumococcus, and had an abscess on one arm from which a pure culture of this organism was recovered. At necropsy, no lesion attributable to the pneumococcus was found in the lung, but a widely disseminated punctate bronchopneumonia in which influenza bacilli played the dominant rôle. The fifth case was a bronchopneumonia secondary to a gangrenous appendicitis with pylephlebitis and abscesses of the liver containing *Staphylococcus aureus* and *Bacillus coli*. The influenza bacillus was the inciting agent of the pneumonia, and the lesions were characteristic grossly and microscopically.

It thus appears in four of the five cases that bronchopneumonia was secondary to another and perhaps prior infection with the pneumococcus. In none of these, however, was there a typical lobar pneumonia, and in one, notwithstanding a blood stream invasion by the pneumococcus, there was no localization of it in the lungs. During the influenza epidemic, when the pneumococcus invaded the lung in association with the



influenza bacillus, there was rarely, if ever, a typical lobar consolidation characteristic of an infection with the former alone, although patches of consolidation could be recognized grossly as produced by pneumococci. It would seem that conditions permitting an infection of the lungs by the influenza bacillus modify at least the extent and distribution of the lesions produced by an associated pneumococcus. In one instance in this series, the pneumococcus infection in the lungs had apparently been overcome, but the lesions due to the influenza bacillus were persistent and progressive and possibly would have resulted in a chronic infection with bronchiectatic cavities.

Following is a brief summary of the clinical histories and pathologic records of these cases.

#### REPORT OF CASES

CASE 1—A colored man, aged 25, a laborer, was admitted to the Allegheny General Hospital, Jan. 2, 1924, complaining of pain in the right side. He gave a history of having had "influenza," in 1918. He had been well until seventeen days before, when he began to have a dull aching in the bones and joints not referable to any particular part. He had developed a cough and expectorated yellowish phlegm. This condition had lasted ten days, then he began to improve markedly. During these ten days, he was up, walking around. The tenth day, he had gone back to work and felt in rather good condition, the thirteenth day after the onset, he had had two chills and became very feverish, on the fourteenth day he had had another chill and developed a sharp pain in the right side on respiration. Following this, he began to cough and expectorated a yellowish material streaked with blood, and had marked dyspnea. He entered the hospital the seventeenth day after the onset.

Physical examination showed him to be a rather thin man with hollow cheeks and a somewhat "drawn" look. The temperature was 102.5 F, the pulse, 135, and respirations were from 28 to 30. There were signs of consolidation involving the lower lobe of the lung on each side. Four days later, he was delirious, and pulmonary involvement was found in the upper and lower lobes on the right and in the lower lobe on the left. He died, the seventh day after entering the hospital and the twenty-fourth day after the onset of illness.

In the hospital, the temperature remained high in the first day, the second and third days it ranged from 99 to 101 F, the fourth day it rose to 105 F, and the seventh and eighth days it reached a lower level again, from 99 to 101 F. The last temperature recorded was 104.5 F, just before death. The pulse was variable but for the most part was rapid, from 100 to 120 and 140. Respirations gradually increased in rate, and remained rapid through the course, from 40 to 50 and 60 a minute.

Laboratory reports showed pneumococcus Type IV in the sputum, a trace of albumin and a few hyaline casts in the urine, red blood counts were 4,500,000, the white blood counts 16,850, and hemoglobin 90 per cent, the day after admission.

At necropsy, a diffuse bronchopneumonia with purulent bronchiolitis involved both lower lobes. The intervening lung was wet and soggy. A thick yellowish white fibrinopurulent exudate bound together the upper and lower lobes posteriorly on the right side. Otherwise, the pleural surfaces were smooth and dark purple. The bronchial lymph nodes were considerably enlarged and soft and the large bronchi and trachea were diffusely reddened with swollen mucosa. The upper lobes were air containing.

Microscopically, the small bronchi and bronchioles were dilated, ulcerated in places, and filled with neutrophilic polymorphonuclear leukocytes. Their walls were thickened, swollen, and the vessels were engorged. Plasma cells and a few round cells infiltrated these walls and the walls of the alveoli. The latter were filled with neutrophilic leukocytes and a good deal of fibrin. These changes gave way to confluent areas of consolidation, where the exudate was essentially leukocytic, thick fluid and fibrin. The pleural exudate was largely layers of fibrin with a few leukocytes and a little hemorrhage. It was organizing in places.

The smears from the lungs showed numerous small short gram-negative bacilli intracellular and extracellular. There were also a few gram-positive cocci. Cultures from the left lung yielded *Bacillus influenzae* and a few colonies of *Staphylococcus albus*. The heart's blood showed no growth.



Fig 1 (Case 1)—Lung showing focal bronchiolar exudate and bronchopneumonia

CASE 2—A colored man, aged 23, entered the Allegheny General Hospital, Jan 2, 1924, complaining of pain in the left side. The past history was unessential. The acute illness began, the day of admission, with aching throughout the body and weakness. That night, he developed pain in the left chest during inspiration. A cough was productive about the time of onset of pleural pain, the sputum being yellowish, later changing to a dirty brown. There was no chill.

Examination proved the patient to be an acutely sick man. The respirations were rapid, 45 a minute, there was no cyanosis, the temperature was 103 F (rectal) and the pulse was 120. There was lagging of the left chest during inspiration. Tactile fremitus was increased below the left scapula. Percussion was dull here, with slightly prolonged expiration and friction rub, but no râles. The heart was negative. Reflexes were present. The abdomen was negative. The systolic blood pressure was 112, diastolic, 60.

Laboratory examination, January 3, showed the red blood count to be 4,200,000, the white blood count, 26,000, the hemoglobin, 80 per cent. The urine examination revealed moderate albumin, numerous hyaline casts and a specific gravity of 1.018.

January 3, the rectal temperature dropped to 98 F, the pulse was 110.

January 4, the patient was very weak, the blood pressure was 90 systolic, 50 diastolic. The rectal temperature rose to 103.5.

January 5, the area of involvement of the left lung was essentially as on admission with a few crackling râles. The systolic blood pressure was 95, the diastolic 60. A sputum culture produced pneumococcus Type IV. A blood culture produced pneumococcus Type II. The temperature range was from 100 to 102 F (rectal), the pulse from 110 to 115, and the respirations were 40. The condition remained essentially the same for several days, until January 8, when râles became numerous over the left base behind, and diarrhea developed, there were from four to five stools a day. The rectal temperature stayed around 102 F, the pulse ranged from 100 to 120. The urine contained much albumin and bile.

January 9, signs of consolidation were made out in the left upper lobe. The diarrhea continued. The systolic blood pressure was 128, the diastolic 55.

The condition remained about the same with, however, lower fever, ranging from 101 F, January 11, to 100, 99 and 98.6 for the next three days. The pulse also was lower, the rate ranging from 90 to 95 a minute. January 13, the whole left lung was found consolidated. Râles were few, and tactile fremitus was decreased. It was concluded that fluid was present in the left pleura, evidence being based primarily on decrease in vocal fremitus. Therefore, January 14, a thoracentesis was performed in the eighth interspace in the midscapular line in the left back. No fluid was found, but a little blood dropped from the needle. The needle was at once withdrawn, and the patient was seized with a coughing spell and expectorated some blood tinged sputum. There was noted a twitching of the left side of the face and an anisocoria, the left pupil was larger than the right. The skin became cold and clammy. The patient collapsed and died in about twenty minutes after puncture, in spite of efforts to revive him.

At necropsy, twenty-eight hours after death, the essential findings were in the lungs. The left lung was found loosely adherent and consolidated throughout with scattered patches of yellowish fibrinous exudate. The pleura was dull everywhere. The lobes were glued together by fresh fibrinous exudate. The lymph nodes in the hilum were tremendously enlarged and swollen. The large bronchi were filled with thick yellowish exudate and bloody mucus. A needle puncture wound was found opposite the thoracentesis wound in the chest wall. The needle penetrated 4.5 cm, and its course was marked out by a ragged hemorrhagic zone from 3 to 4 mm wide. The puncture wound also involved several smaller vessels in the deeper portion of the lung. On section, the surface of consolidated lung had numerous small yellowish patches from 2 to 3 mm across, slightly elevated and bronchial in distribution. From some of the larger areas, pus exuded. The intervening lung substance was somewhat granular, light red in the lower lobe and with grayish patches in the upper lobe. The bronchial pus pockets were less numerous in the grayish areas of the upper lobe.

Microscopically, there were small bronchiectatic abscesses with surrounding consolidated lung. Elsewhere, the bronchi and bronchioles had ulcerated and were filled with leukocytes. The interstitial tissue and bronchial walls were generally thickened and infiltrated with numerous plasma cells. The alveoli contained in places much fibrin and many leukocytes, elsewhere very little, aside from a few large pale mononuclears and a little fluid. Hemorrhage was plentiful in the fresher exudate, and the capillaries were everywhere engorged. Patches of hyperplasia of adjacent alveolar epithelium were seen here and there, the lymph vessels were thrombosed, and in some there was organization. The surrounding and adjacent areas of the lung showed a rather diffuse pneumococcus type of consolidation. The pleural exudate was thin, fibrinopurulent, and organizing in places. The air containing lung tissue was emphysematous.

Sections through the needle injury showed hemorrhage, with acute thrombosis of a large vein into which lung tissue had been pushed

Smears from the bronchial and lung exudate contained many tiny gram-negative bacilli, intracellular and extracellular, probably influenza bacilli. There were also a few organisms present with the morphology of pneumococcus. There was no growth in the cultured heart's blood. From the pus of the bronchial exudate *Bacillus influenzae* grew out, but no pneumococci.

CASE 3—A white man, aged 57, was admitted to the Allegheny General Hospital, Jan 8, 1924, complaining of "sickness in his stomach." The patient dated his illness to Christmas day, 1923, at which time he had started his last spree. He had consumed considerable hard liquor every day up to admission. He began vomiting a few days before admission, and a heavy pain developed in the upper part of the abdomen accompanied by a "chilly feeling." No definite chill, however, was recorded.

Physical examination, on admission showed the temperature to be 101 F, the systolic blood pressure was 128, diastolic 80. The patient was described as a sweating old man. The chest was negative aside from emphysema. The heart was not enlarged and was regular. There was marked pain in the epigastrium, but no masses.

Laboratory reports, on admission, revealed that the urine was clear, the specific gravity was 1.028, there was a trace of albumin, and a few hyaline casts. The red blood cells totaled 4,800,000, the white blood cells, 9,000, the hemoglobin was 90 per cent.

While in the hospital, twenty days, the patient ran a septic temperature, generally high in the evening and low, often normal, in the morning. During many days, the range was from 100 to 103 F (day of admission), from 98.6 to 102, and from 100 to 103. Toward the last week or ten days, the temperature was constantly high from 101 to 103 and 105. The pulse ranged from 80 to 90 and 100, occasionally reaching 120.

The patient was at times delirious, and it was thought at one time that there was an early lobar pneumonia, particularly in view of positive blood and sputum cultures for the Type III pneumococcus, January 14. January 15, *B. influenzae* was recovered from the sputum together with the Type III pneumococcus. There was no improvement in the general condition, and the patient finally died twenty days after admission.

At necropsy, the lungs showed very small peribronchial areas of consolidation, and were otherwise air containing but emphysematous. Microscopically, however, the pneumonia was found to be an interstitial bronchopneumonia characteristic of the influenza bacillus. The bronchioles and small bronchi in places had an ulcerated lining with organization of the contained fibrinopurulent exudate. In some, a fresh purulent exudate alone was found, in others, a little intermixed with fresh blood. The bronchial walls and adjacent alveolar walls were thickened and infiltrated with plasma cells and neutrophilic leukocytes. The latter cells, with desquamated epithelium, filled the surrounding alveoli. Fibrin was not abundant. In some areas, there was nothing more than a purulent bronchitis without consolidation of the surrounding alveoli. Some intracellular influenza bacilli were easily demonstrated. The lung was generally emphysematous.

A large supradeltoid abscess of the right arm was found and the pus contained a pure culture of Type III pneumococcus. There was also an acute intracapillary glomerular nephritis, atrophy of the cerebral cortex, osteitis deformans of a moderate degree and other chronic alterations of no essential interest here.

Smears from the abscess pus contained gram-positive cocci. A culture from the pus and from the heart's blood contained pneumococcus Type III in both. The lungs were not cultured.

CASE 4—A white man, aged 22, was admitted to the Allegheny General Hospital, Jan 30, 1924, complaining of pain in the abdomen, and vomiting. The past history was unessential. The patient had been examined by an attending physician, several days prior to his admission, who found a bronchopneumonia of the right lower lobe. At that time, the patient had a certain amount of abdominal discomfort which, in a few days, became more and more severe. Acute appendicitis was suspected, and the patient was sent into the hospital. He gave a rather typical history of acute appendicitis beginning with epigastric pain, three days before admission, the pain promptly localized, however, in the right lower quadrant, vomiting developed, later, he became constipated. Pulmonary symptoms apparently were unimportant on admission, and none were recorded.

Physical examination revealed indefinite signs at both bases, but pneumonia apparently was not suspected or at least was not recorded. There was pain and rigidity in the right lower quadrant. The temperature, on admission, was 102 F, the pulse was 95 and the respirations 20. The patient was acutely ill, and acute appendicitis was considered the major cause.

Laboratory reports on admission gave the number of white blood cells as 17,900. The urine showed a trace of albumin and a few hyaline casts.

Under nitrous oxid and gas anesthesia, January 31, the acutely infected and gangrenous appendix was removed, drains were inserted, and the incision was partially closed.

February 1, there were definite signs of consolidation of the right lower lobe. The temperature rose from 102 to 104 F, the pulse from 90 to 120.

February 2, the temperature continued high, ranging from 99.5 to 103 and 104 F, and two days before death it ranged from 102 to 105. At the same time, the pulse became rapid and stayed above 120, later gradually reaching from 130 to 140. The respirations were rapid, from 30 to 40 and 45 a minute.

The patient continued to do badly with a large amount of discharge from the operative wound. February 6, there was a severe hemorrhage from the wound, and the patient promptly died.

Necropsy was done two and one-half hours after death. The right lung was found consolidated in patches with thin fibrinous exudate over the surface. The pleura of the lower lobe was purple and dull, elsewhere, it was gray and glistening. The lymph nodes of the hilum were not enlarged. The lung was partially air containing. On section, in both upper and lower lobes, one found numerous small yellowish opaque spots, bronchial in distribution and slightly elevated above the general cut surface with a small portion of surrounding consolidated lung. There were also areas of hemorrhage. The entire lung was wet and heavy. Small areas were easily palpated. From certain of the larger bronchi, pus escaped, the intervening lung was dark purple.

The other lung was free from such changes and was air containing throughout.

In addition, there was found an acute peritonitis in the right lower quadrant and an ascending pyelophlebitis. The small veins of the mesentery leading from the appendix and cecum were filled with pus. In the liver, small abscesses in the portal veins were quite numerous. There was a large suppurating thrombus mass in the portal vein where it joined the splenic. The splenic vein and the veins draining the greater portion of the intestine were, however, free from pus or thromboses.

Microscopically, the pneumonia was bronchial in distribution. The bronchi and bronchioles were dilated and filled with a fresh leukocytic exudate. The walls of the small bronchi and bronchioles were infiltrated with plasma and other mononuclear cells and fibrin, which extended into the surrounding alveolar walls. The lining of the air channels in places was found ulcerated and contained an organizing fibrinopurulent exudate. The alveoli contained a cellular and fibrinous exudate made up largely of neutrophilic polymorphonuclear leukocytes and a few large phagocytic mononuclear cells. There was also

much hemorrhage, and the vessels were generally engorged. There was hyperplasia here and there of alveolar epithelium, which was found in large clumps and masses. In a wider zone, hemorrhage was more conspicuous, but cellular exudate was essentially the same. Many patches of pneumonia were undergoing organization. In the leukocytes, many tiny influenza bacilli were found. This case was apparently a pure influenza pneumonia of some duration. The staphylococcus found in the lung can be explained as a result of the bacteremia with this coccus, as there is no evidence of a staphylococcus lung infection.

*Staphylococcus aureus* and *Bacillus coli* were recovered from the peritoneal exudate. Gram-positive cocci and gram-negative bacilli also were found in the pus of the liver abscesses, but cultures were negative. Gram-positive cocci

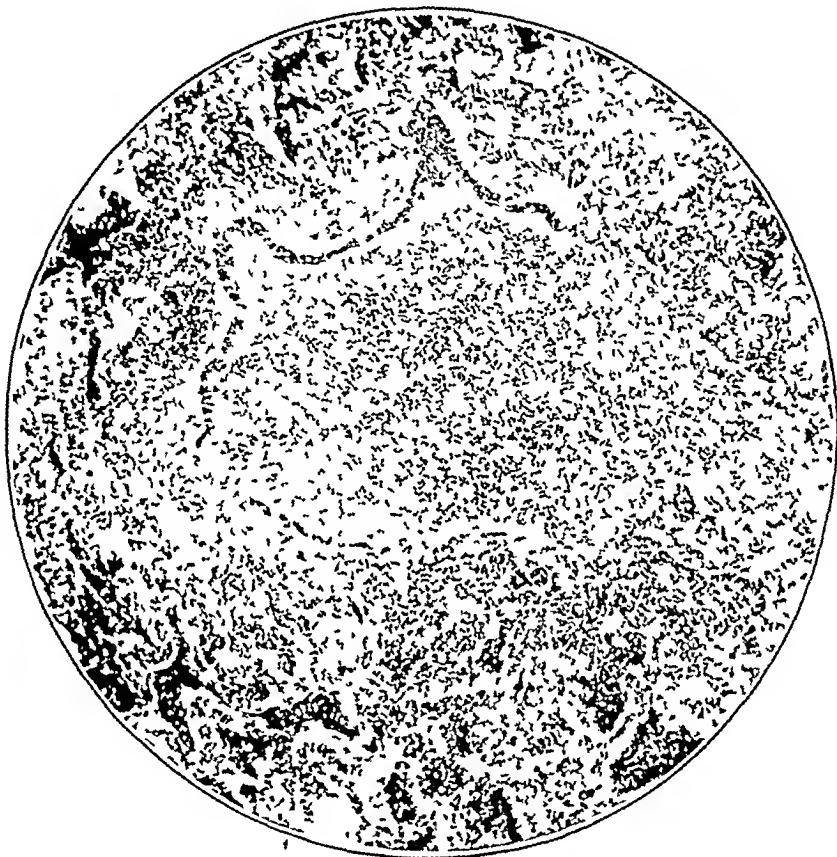


Fig 2 (Case 5) —Bronchiole dilated, ulcerated and filled with pus, fibrinous exudate in surrounding alveoli, and mononuclear exudate in bronchiolar wall

and gram-negative bacilli were seen in pus from the lung, but only the coccus, which proved to be *Staphylococcus aureus*, grew out. *Staphylococcus aureus* was found in the blood by culture.

CASE 5—A colored man, aged 23, entered the Allegheny General Hospital, Feb 6, 1924, complaining of pain in his right side. The past history was unessential. The patient had been well until February 1, when he had developed a general malaise and discomfort in the right chest. Two days later, he had had a distinct chill and coughed up a good deal of yellowish sputum. The pain in the chest during respiration had developed at the same time, and, about the same time, there had been marked dyspnea.

On examination, six days after onset, the temperature was 103 F, the pulse was 120, and respirations were 68. There was anisocoria (the right pupil being larger than the left) and typical signs of consolidation of the middle and lower lobes of the right lung. The heart was negative, the abdomen was distended, and reflexes were sluggish.

Laboratory reports, on admission, were that the urine was acid, the specific gravity was 1.020, there was a heavy cloud of albumin and many red blood cells and hyaline casts. The red blood cells totaled 4,300,000, the white blood cells, 15,560, the hemoglobin was 80 per cent.

The temperature ranged from 103 to 104 F, the pulse was from 120 to 130 and the respirations were from 50 to 68.

The second day in the hospital, February 7, the patient's condition was poor, with signs of extension of the pneumonia to the upper right lobe. The systolic blood pressure was 120, the diastolic 75. The blood culture contained a Type IV pneumococcus. The fever continued high, from 104 to 105 F, with rapid pulse and respirations.

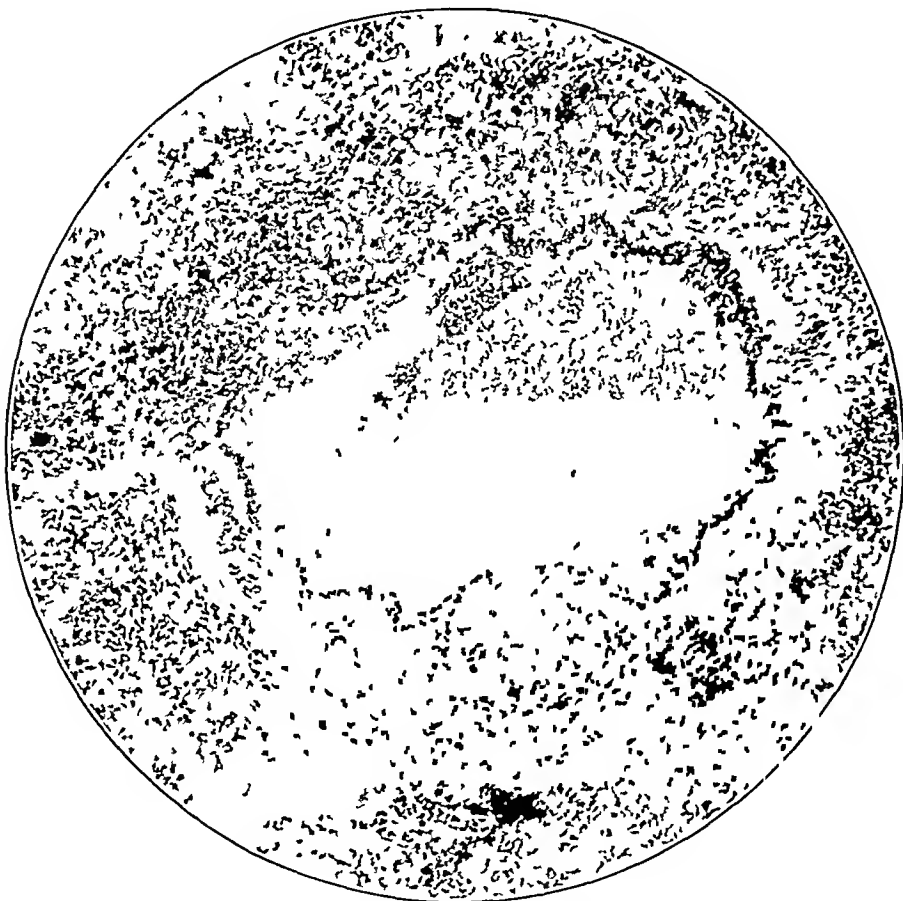


Fig 3 (Case 5) —Bronchiole dilated and filled with pus, peribronchiolar infiltration by mononuclear cells

The patient died, the third day in the hospital.

At necropsy, both lungs were found partially consolidated with fibrinous and bloody exudate and adherent surfaces. The hilum nodes were swollen, and the bronchial mucosa was markedly reddened and swollen. The bronchi contained much frothy fluid. In the right lung, on section, a gray patch of consolidation was found near the hilum, and it merged into a soft, boggy, reddened surrounding tissue. A second large patch of red consolidation was found in the base on the median side. It gradually faded into the surrounding pink lung. On further sectioning, these irregular patches were found to extend through the upper and lower lobes with here and there other areas. The intervening lung was generally soggy. In the latter areas, one found small peribronchial areas

of consolidation. In the inferior lobe of the left lung were found similar patches of consolidation. The upper lobe was air containing. The other gross findings were unimportant.

In sections, the small bronchi and bronchioles were filled with pus, but were not particularly distended. Here and there, the air passages had ulcerated, and purulent exudate was adherent to the denuded surfaces. The swollen walls were infiltrated with plasma cells and leukocytes, and the vessels were engorged. The surrounding alveoli were filled with leukocytes, large mononuclear cells and fibrin, also a good deal of fluid in places, and the walls were necrotic in places. Peribronchial hemorrhages were found. The intervening lung tissue was filled with fluid with from a few to many cells and some hemorrhage. In sections from the larger consolidated areas, one found similar bronchial changes, but the striking feature was the polymorphonuclear and fibrinous exudate filling the alveoli, characteristic of the pneumococcus. Scattered through all sections, a fair number of large mononuclear and plasma cells were found. The pleural exudate was fibrinopurulent. Small gram-negative bacilli, morphologically like *Bacillus influenzae*, were found in the bronchial exudate of the focal areas.

#### CHARACTERISTIC PATHOLOGY

The gross pathology of the lungs in these cases was characteristic and corresponded to descriptions of the pneumonias caused by the influenza bacillus, as recorded by Pfeiffer in so-called recurrences of epidemic influenza in 1890-1892, and by Wolbach,<sup>3</sup> MacCallum,<sup>2</sup> Goodpasture and Burnett<sup>4</sup> and others, during the pandemic of 1918. Since there is no evidence of a concurrent infection simulating epidemic influenza accompanying the onset of the present infections with *B. influenzae*, it seems possible to draw definite conclusions as to the lesions produced by this bacillus without this complication, and, in this way, a clearer idea may be gained of its pathogenicity and a better estimate of its importance as an agent in the recent pandemic of influenza.

*Gross Appearance of the Lungs*—In no instance was there a notable excess of fluid in the pleural cavities. The involved lobes were moderately voluminous, felt fairly uniformly consolidated, and presented usually a smooth, purple, moist pleural surface. In those portions in which the pneumococcus was active, there was superimposed the usual shaggy fibrinopurulent exudate. But this was a minor feature, even in a lobe completely consolidated by exudate of the kind associated with pneumococcus infection. On the cut surface, an entire lobe presented a quite uniform change. Almost every bronchiole was outlined distinctly by a gray zone of consolidation, from 1 to 3 mm in diameter. The bronchiole in the center of the patch seemed to be distended with a droplet of yellow pus, and similar pus could be expressed from the

<sup>3</sup> Wolbach, S. B. Bull. Johns Hopkins Hosp. **30** 104 (April) 1919.

<sup>4</sup> Goodpasture, E. W., and Burnett, F. L. U. S. Nav. M. Bull. **13** 177 (April) 1919.



small bronchi. The intervening alveoli were usually filled with sero-purulent or hemorrhagic exudate, so that there was very little air containing tissue in the involved lobe. In one case, this interbronchiolar exudate was not present, and, in another, the lobes thus involved were filled with blood, obscuring, in the more central portions, the peribronchiolar nodules which were quite conspicuous about the periphery.

The distinctive feature of the gross appearance was the gray peribronchiolar areas of consolidation with a semifluid yellow pus within the lumina of the bronchial tree. These nodules were not hard and only slightly elevated. This appearance of a lung may be relied on, we believe, in diagnosing an influenza bacillus pneumonia from the gross specimen. Smears from a droplet of pus in the bronchial tree show great numbers of small gram-negative bacilli within leukocytes or extracellular. The type of alveolar exudate and its extent varies in different cases, and the influenza bacillus may cause a diffuse purulent exudate, in certain instances, as was exhibited in one of the cases under consideration, which obscures the characteristic peribronchiolar nodules.

*Microscopic Appearance*—The inflammation is quite distinctive. The smaller bronchi and bronchioles appear to be dilated, and their lumina are filled with plugs of closely packed polymorphonuclear leukocytes. Characteristically, the mucous membrane of bronchioles is ulcerated in places and covered, at these points, by a fibrinous exudate. The bronchial and bronchiolar walls conspicuously contain a cellular exudate and are thickened. In early stages, polymorphonuclear leukocytes are the most numerous, later, they are replaced by cells of the lymphocytic series, the characteristic type being a rather large basophilic variety which resembles the plasma cell, but is usually larger. These can be found in mitosis locally. Smaller lymphocytes are present in varying numbers.

The alveolar walls immediately surrounding the involved bronchi and bronchioles seem compressed laterally, and are filled with plugs of dense fibrin with little or no cellular exudate. The alveoli, at the termination and about the bronchioles, are filled with a polymorphonuclear cell exudate with little fibrin. The changes in intervening alveoli vary. In one case, they were air containing, the lesion being rather sharply restricted about terminations of the bronchial tree, in another there was extensive hemorrhage, involving a large part of a lobe, in another, there were focal areas of necrosis of alveolar walls, circumscribed hemorrhages and a more or less diffuse serous and purulent exudate. Fibrin was inconspicuous, except in alveoli immediately about the bronchi and their terminations, where it constituted an essential part of the microscopic picture. While it was evident that

an infection by the influenza bacillus could produce destructive changes of alveolar walls, with a variable exudate within them, there did not appear to be any change in these intervening structures which was constant or typical for such an infection. The walls of the larger bronchi and the mucosa of the trachea presented varying degrees of inflammatory change, but never so severe as that in the terminal air tubes. In no case was there found a hyalinized fibrinous membrane lining the alveolar ducts, such as was found during the recent pandemic.

*Changes in Other Organs and Tissues*—The bronchial lymph nodes were enlarged and succulent. Microscopically, in these nodes and in the splenic pulp, there was active mitosis of the cells of the lymphocytic series, with the production of numerous basophilic forms like those found in bronchial walls. Similar cells were present also in noticeable numbers within sinuses in the liver. The spleen was of normal size or only slightly enlarged. It might contain small hemorrhages.

The kidneys presented no change other than parenchymatous degeneration, except in Case 5, in which there was an intracapillary glomerular nephritis. In Case 1, which appeared to be essentially an influenza bacillus infection, although there was a pneumococcus pleuritis in one area, small focal myocardial necroses were present in sections of the left ventricle.

The suprarenal glands, in two instances, showed extensive parenchymatous degeneration particularly in the fascicular zone, but no actual necrosis.

The testes, in two cases, showed a condition of aspermatogenesis with shrinking of seminiferous tubules, such as has been described in association with influenza. Otherwise, no changes worthy of note were encountered outside the respiratory system.

*Comparison of Pathologic Anatomy with that of Fatal Cases of Influenza Associated with an Influenza Bacillus Pneumonia During Pandemic of 1918*—The pathology of the five cases described differed grossly from that seen in the epidemic with a pneumonia of comparable duration, in the absence superficially of cyanosis, subcutaneous emphysema, and necrosis of abdominal rectus muscles. There was a conspicuous absence of the wet, boggy frothy condition of the lungs and of the spongy appearance caused by dilatation of alveolar ducts. Fluid exudate was not so prominent. Interstitial emphysema was not observed. Microscopically, the lesions produced by the influenza bacillus, in the lungs of these patients, seem identical with those found, during the epidemic, in association with this micro-organism, with the exception of the acute toxic stage, consisting of dilated alveolar ducts, the deposition of a hyaline membrane and an exudation of fluid. These acute lesions have been considered by several pathologists to be

independent of the bacterial invasion of the lung, as ordinarily found, and have been attributed, especially by Wolbach and Frothingham<sup>5</sup> and by Goodpasture,<sup>6</sup> to the virus of influenza, which is considered by them as an infectious agent distinct from the influenza bacillus and other secondary invaders of the lung. The absence, in these cases, of a toxemia comparable to that of epidemic influenza and of lesions attributable to an intoxication, such as necrosis of striated muscle, the characteristic acute changes in the lungs and necrosis of the suprarenals, may be considered as further evidence of a complete etiologic independence of epidemic influenza, the influenza bacillus present in certain cases being one of the many secondary invaders that attack the stricken individual.

The influenza bacillus in acutely infecting the lungs, as found in these five cases, does not alone cause a dilatation of alveolar ducts and a partial lining of them by a hyaline membrane, associated with a serous exudate. Since this lesion was found as a part of the pneumonic process in early stages of pneumonia accompanying influenza in 1918, it has not been observed by the writers in any condition of the lung of whatever etiology, until quite recently it was found characteristically in two cases, and under circumstances which have enabled us to formulate an opinion as to its nature and the conditions under which it may be brought about.

CASE 6—A boy, aged 9, died of a hemolytic streptococcus bacteremia following an acute mastoiditis and septic thrombosis of the internal jugular vein on the right side. The lungs presented many small areas of embolic pneumonia, in which streptococci were present, evidently arising from emboli from the thrombosed jugular vein. These lesions were circumscribed, and intervening alveoli were little affected. There was no passive congestion. In one microscopic section of the lung, there was a wedge shaped area with its base measuring 1 cm. at the periphery. In this area, the alveoli were filled with a serous exudate in which delicate strands of fibrin had formed. The alveolar ducts were dilated, and on their walls and those of certain neighboring alveoli was a hyaline membrane in every way identical in appearance with that previously seen in the pneumonia of influenza. Within this area, there was no evidence of a primary bronchial infection which might have played a part in its formation. No similar condition was present in other portions of the lung.

It seemed evident from an examination of this specimen that the lesion in question may be brought about independently of a primary bronchial infection. The shape of the area suggested its dependence on an interference with the vascular supply of the part, and the circumstances were such that it seemed probable that an embolus from the jugular vein had recently intercepted the branch of the pulmonary artery supplying it, resulting in an injury to the capillary bed with an exudation of fluid containing a certain amount of fibrogen. Fibrin was probably rapidly formed, and the serum that poured freely into the alveolar ducts could flow out leaving strands of fibrin which adhered to the

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5 Wolbach, S. B., and Frothingham, C. Influenza Epidemic at Camp Devens in 1918, Study of Pathology of Fatal Cases, *Arch Int Med* **32** 571 (Oct.) 1923.

6 Goodpasture, E. W. *Am J Med Sc* **158** 863 (Dec.) 1919.

walls and became fused. Fibrin, under these conditions, as in the hyaline membrane of diphtheria, may lose its fibrillar structure and characteristic staining reactions.

CASE 7—A white girl, aged 25, had been in the Allegheny General Hospital on two admissions. The first time, she entered primarily because of an acute pelvic inflammatory disease. While she was in the hospital, it was discovered that there was an extensive left sided pleural effusion, which, however, was not drained. There were no respiratory symptoms recorded, and after the pelvic inflammatory disease subsided, she went home.

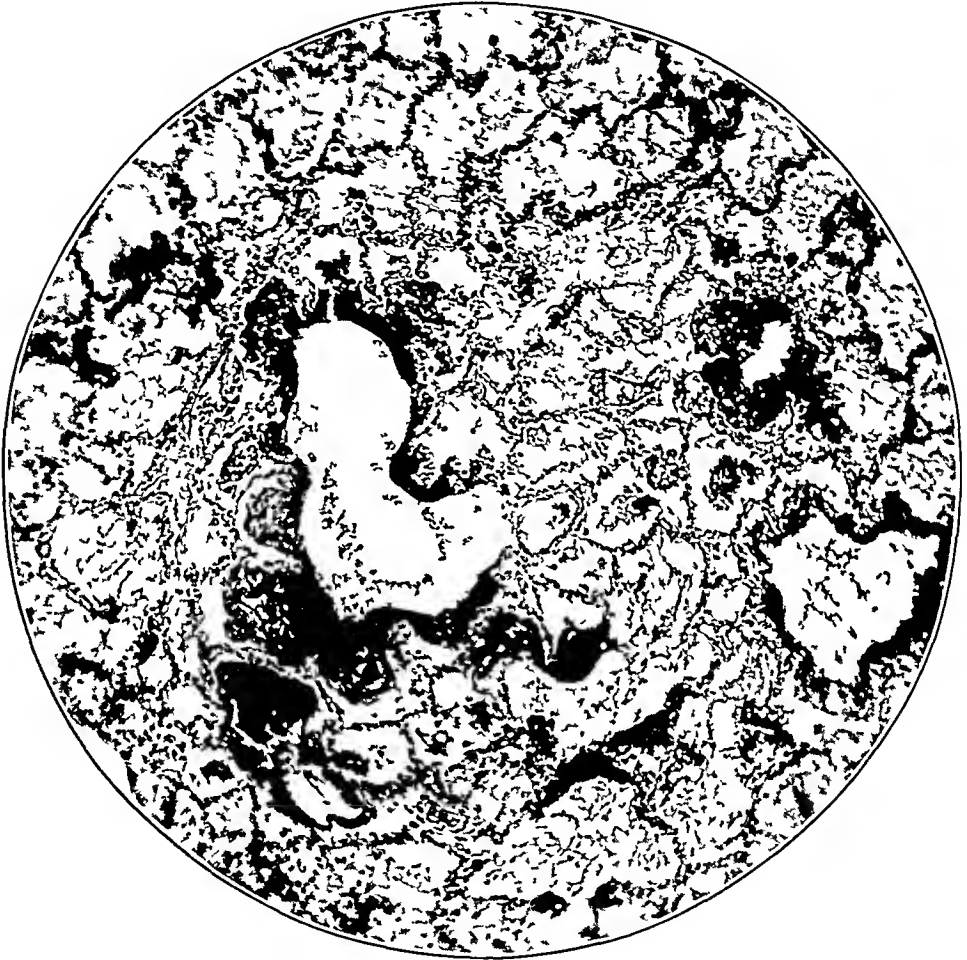


Fig 4 (Case 6)—Hyaline membrane lining alveolar ducts and alveolar walls, absence of cellular exudate, serum and delicate strands of fibrin fill the alveoli.

The patient entered the hospital a month after discharge with marked symptoms, namely, dyspnea, cyanosis, and edema of the left side of the body. There were definite signs of fluid in the left pleural cavity. The thorax was tapped, and 1,000 c.c. of turbid fluid removed. Two days later, she died. There was a marked tachycardia during both admissions, the rate being 110, 120, 130 and 140 while she was in bed. The temperature reached 100 F only twice during the first admission, generally ranging from 98 to 99 and 99.5. During the second admission the temperature was from 98 to 102.

At necropsy two hours after death, the left side of the face, most of the neck, left chest, left arm and forearm, and to a slight extent the hand, showed a marked brawny edema. The thoracic cavity and pericardial sac were filled with

a cloudy fluid The left lung was completely atelectatic, and the right partially so with patches of apparent consolidation in all lobes The right auricle was dilated, and the heart otherwise, in the gross, was negative The large thoracic veins were engorged The thyroid gland was greatly enlarged and completely surrounded the trachea The enlargement was due primarily to multiple adenomas, from eight to ten in number, ranging in size from 0.75 mm to 3 cm across The trachea was compressed The blood vessels of the arm and neck were not engorged Edema, in the gross, appeared to be due to a lymphatic obstruction There was evidence of a low grade pelvic peritonitis Gross findings were otherwise unessential

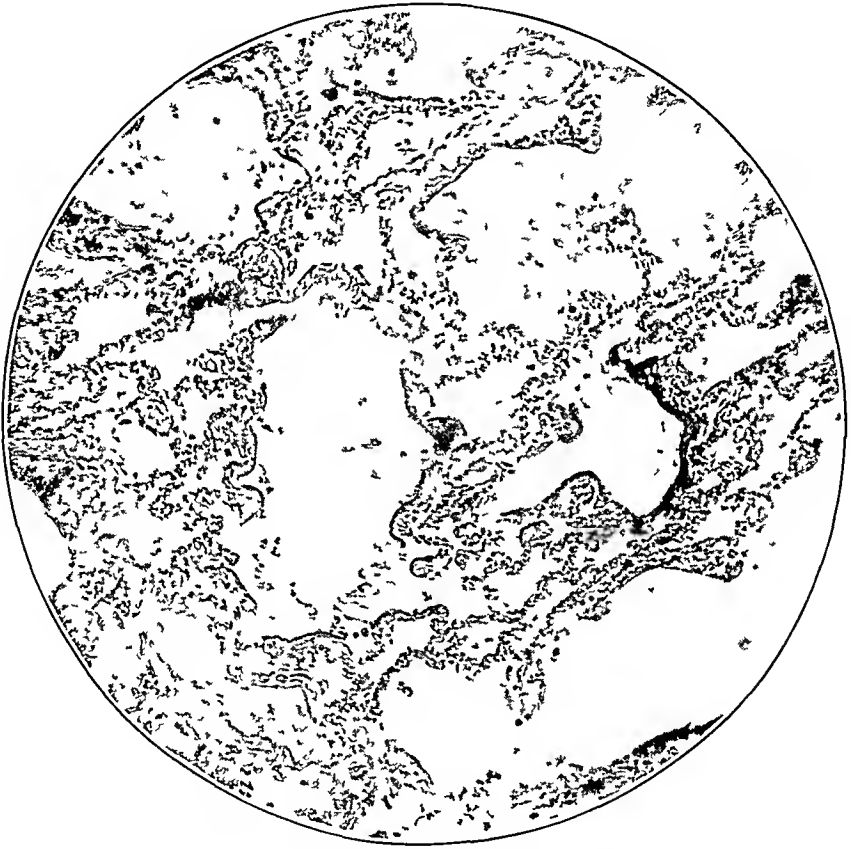


Fig 5 (Case 7) —Hyaline membrane on walls of alveolar ducts, no cellular exudate

Microscopic examination revealed that, in the right lung, there was no evidence of pneumonia in the ordinary sense The alveoli were packed in large areas by large phagocytic fat containing mononuclear cells, with here and there a few scattered neutrophilic polymorphonuclear leukocytes The alveolar walls were found thickened, and the lining cells were undergoing proliferation These changes were most conspicuous about the bronchioles The alveolar walls contained in places plasma cells, and about some of the air passages were round cells There was evidence of organization of the alveolar exudate in places, no fresh fibrin was found Another striking feature was a widespread hyalinized membrane lining the distended alveolar ducts and adjacent alveoli The membrane was identical with the one found in the lung of the boy described above The hyalinized membrane did not show the fibrin reaction with phosphotungstic acid There was also more or less coagulated thick serous exudate with a few cells in many of the alveoli

apparently representing a more acute and advancing lesion. There was very little evidence to indicate that the lesion started in the bronchi or bronchioles, as they contained very little exudate and this was widely scattered and the epithelial linings were intact. The capillaries contained from a few to many leukocytes, and some were thrombosed. One fair sized pulmonary artery was found with a partially occluding organizing thrombus. The sections from the left lung showed typical atelectasis, there was no hyalinized membrane. The myocardium from the right and left ventricles contained a good deal of fat, areas of focal necrosis, and fibrosed patches.

#### COMMENT

The occurrence of this lesion, it seems, may depend entirely on a mild injury to the capillary bed in a part of the lung, and the possibility is suggested that in influenza, in certain of the more severely intoxicated individuals, such an injury may have resulted from a circulating toxic agent which acted injuriously on the capillary bed of the lung from within, as it must have injured also the abdominal rectus muscles, which not infrequently became necrotic and ruptured. This explanation would make this initial pulmonary lesion a part of influenza itself, and would provide an anatomic basis for the favorable conditions that undoubtedly existed for secondary invasions of the lung by various types of bacteria, including *Bacillus influenzae*, and evidence is accumulating that there is a primary influenzal injury and inflammation in the complicated pathologic process that constituted the pneumonias of the recent pandemic.

A study of the group of cases which we have described does not show that the influenza bacillus can initiate an infection of the respiratory tract in adults. Always there was an accompanying infection, usually by the pneumococcus, which may have been the first infection preparing the way for the influenza bacillus. When once the influenza bacillus gains a foothold within the lungs, it is very pathogenic and causes a characteristic pneumonia, which may be fatal.

The influenza bacillus is very frequently present in secretions from various kinds of respiratory infections, yet it has rarely been reported in fatal acute bronchopneumonias in adults. In an epidemic of an acute respiratory infection in Chicago, in 1908, Davis<sup>7</sup> cultured the bronchial exudate from twenty-six cases complicated by bronchopneumonia and found the influenza bacillus in ten instances, in most of which they were the predominating organism. The influenza bacillus apparently played no part in initiating that epidemic, but appeared late in the disease and always in association with other organisms, such as the pneumococcus and streptococcus.

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<sup>7</sup> Davis, D. J. Influenza and Influenzal Pneumonia, Arch. Int. Med. 2: 124 (Sept.) 1908, J. Inf. Dis. 10: 259, 1912.

## CONCLUSIONS

1 The influenza bacillus may be an important agent in the production of bronchopneumonia in adults during a period in which there is no evidence of an epidemic of influenza

2 It usually invades the lung in association with infections by the pneumococcus or other bacteria which were probably the primary agencies of the disease in which the influenza bacilli were found

3 The influenza bacillus produces characteristic lesions in the lung, recognizable grossly and microscopically The lesion is essentially a bronchitis, ulcerative bronchiolitis, and bronchopneumonia with a tendency to chronicity and to the formation of bronchiectatic abscesses

4 Acute infections with an influenza bacillus may not be associated at any stage with a profound toxemia, nor may there be lesions of toxic origin, as were found in the pneumonias of the influenza pandemic of 1918

5 The influenza bacillus is to be considered as one of the important secondary invaders of the lung causing a bronchopneumonia which may terminate fatally

6 The hyaline membrane that occurred so characteristically in early influenzal pneumonia in the past pandemic has been demonstrated typically in two cases in which an influenzal infection could have played no part This lesion is probably due to an injury to the pulmonary capillary bed, and its frequency in influenza is attributed to a toxic injury to the capillaries of the lung from a circulating poison generated by the etiologic agent of this disease

# FAMILIAL BLOOD DYSCRASIAS <sup>†</sup>

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AND

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Familial blood diseases are, in many instances, directly related to the hemolytopoietic system, the special pathology of which is but meagerly understood. The physiologic activity of this system controls the cellular elements of the blood by maintaining a proper balance between blood cell formation and destruction.

The reticulo-endothelial system would seem to comprise the most important portion of the hemolytopoietic mechanism, and consists of the endothelium and related reticular cells of the spleen, lymph and hemolymph glands, the star cells of the liver and the reticulo-endothelium of the bone marrow. The large, wandering endothelial cells are best considered in this system. In the embryo, the liver and spleen contribute to the formation of red blood cells, whereas in postnatal life the bone marrow constitutes the essential seat of the formation of most of the cellular blood elements, unless protracted strain causes a reversion to the embryonic functions of red and white cell formation. Normally, the greater part of the hemolysis of the red cells takes place in the spleen, but under abnormal conditions the hemocidal process becomes excessive in other parts of the reticulo-endothelial apparatus. The endothelial cells which line the blood spaces probably function in a unique way in this respect. The blood making organs or hemopoietic system are a specialized part of the reticulo-endothelial system. Such a conception is tenable with Maximow's theory of the origin of primitive blood cells, which result from differentiated endothelial cells in the area vasculosa of the developing embryo.

Gaucher's familial splenomegaly seems quite definitely related to an abnormal reticulo-endothelium system, if we assume that the large pathologic Gaucher's cells are of endothelial origin. Familial hemolytic jaundice, on the other hand, seems quite definitely related to abnormal hemolysis within the same system. Less obvious, however, in relation to the physiologic pathology of the hemolytopoietic system, are certain family anemias and certain familial splenomegalies.

Efforts at proving a constitutional disposition toward certain disease must necessarily eliminate common toxic and infectious factors. With

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such an approach in mind, family disease as such presents a degree of clinical proof of constitutional disposition toward that disease. More specifically, we speak of a constitutional asthenia of the bone marrow in certain blood dyscrasias, realizing we so speak in the abstract. Likewise, we speak in the abstract when referring to certain families predisposed to early hypertension and arteriosclerosis but clinical experience causes us to respect such terms. There is no explanation other than "In the makeup of the machine bad material was used for the tubing" (Osler).

It seems important to review briefly the field of family blood abnormalities and to report and discuss a few cases recently studied. The future will decide the part constitutional disposition plays in certain blood dyscrasias, only after entire families have been intensively studied.

#### FAMILIAL AND ACQUIRED HEMOLYTIC ICTERUS

In this malady the brilliant results of splenectomy leads one to suspect that the primary causative factor lies in the hemolytopoietic mechanism, the spleen being an essential factor in the pathogenesis. On the contrary, it is noted that the fragility of the erythrocytes does not always return to normal after splenectomy, this fact adds weight to a primary involvement in the structure of the red blood cell. Excluding an infectious group, two types of hemolytic jaundice are recognized. One, the congenital form which may involve families for three or four generations, but does not seem to follow the mendelian law of dominant and recessive characters, a second, the acquired idiopathic type, which makes itself manifest usually in adult life and produces symptoms of a graver character. In the acquired type, however, the pathogenesis is probably similar to the congenital form with the exception of recently reported hemolysins in the serum which need more intensive study, especially during the crises. Many congenital patients complain of few discomforts save jaundice. Others of the same family may suffer more intensively, even to a point where splenectomy is indicated, some members may escape the disease entirely.

The symptoms depend primarily on the degree of hemolysis present. Patients with mild types complain of an abnormal icteric color, slight anemia and some loss of strength. Patients with severe types, however, suffer from intermittent crises of deglobulization, paroxysmal massive red cell destruction. These attacks are evidenced by malaise, headache, vomiting, abdominal pain, rapid enlargement of the spleen, anemia and urobilinuria. The morphologic character of the red cells shows evidence of rapid destruction, microcytes and tailed cells. Compensation by the marrow as an offset for the blood loss is manifested particularly by an abnormal percentage of reticulated cells, occasional nucleated red cells, polychromatophilic cells, leukocytosis and an increase in the blood

plates With a rising hemolytopoietic balance (Schneider <sup>1</sup> and Krumbhaar <sup>2</sup>) little anemia persists With a lost hemolytopoietic balance, however, a severe anemia results Splenectomy is offered as a means of relief for those individual patients ill enough to be handicapped by their condition

Histopathologic sections of spleens removed have shown no specific changes Congestion of the splenic pulp and dilatation of the sinusoids

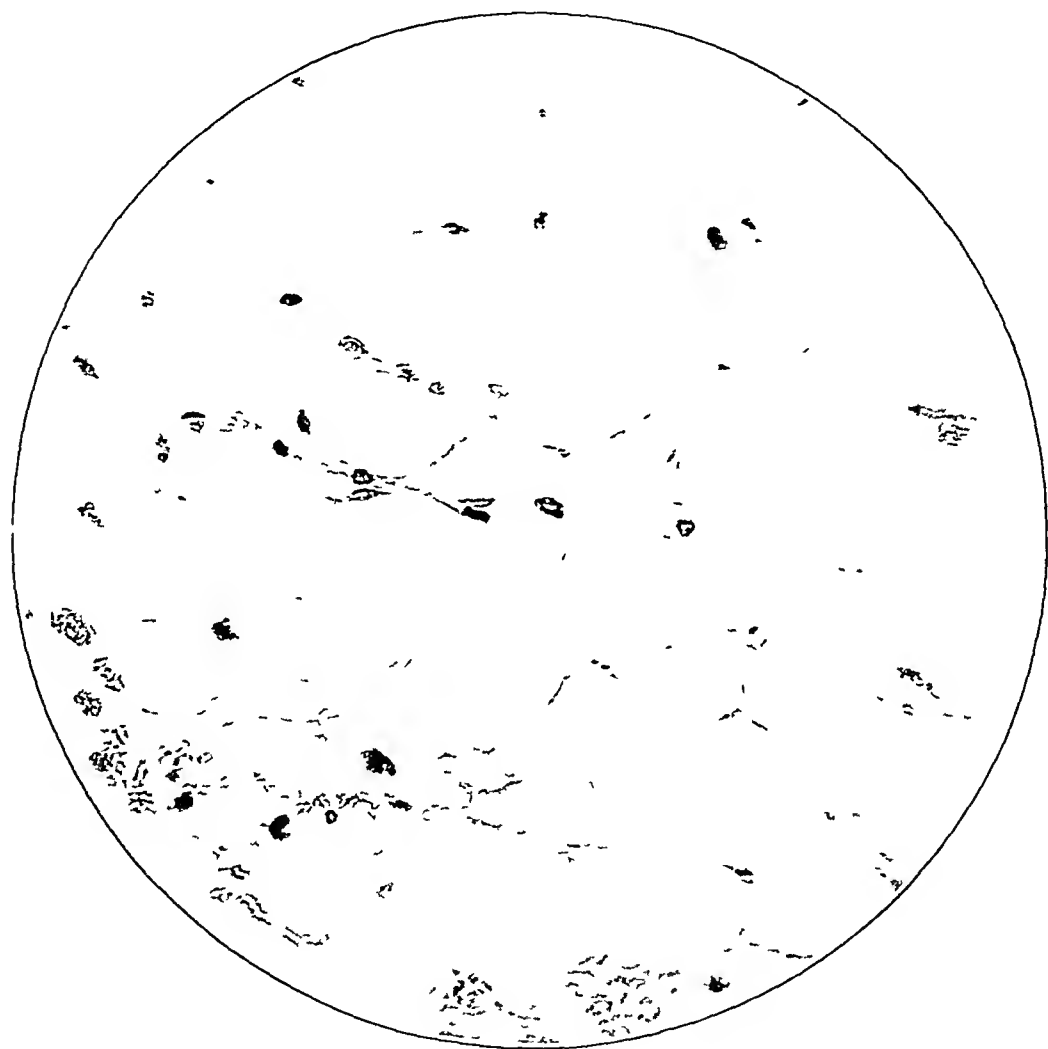


Fig 1—Section of tibia marrow The cellular activity here shown is considered approximately normal for a young adult Death occurred during a severe asthmatic attack

are the outstanding features Most spleens are enormously enlarged The capsules usually present evidences of perisplenitis Both the liver and bone marrow contain much hemosiderin The marrow is hyper-

1 Schneider, J P Further Quantitative Study of the Duodenal Blood Derived Pigments, *Arch Int Med* **19** 156 (Jan) 1917

2 Krumbhaar, E B *Am J M Sc* **166** 329 (Sept) 1923

plastic Calculi are common in the gallbladder A recapitulation of modern views on hemolytic icterus is given by Tileston<sup>3</sup>

The family grouped below illustrates a type of family acholuric jaundice, which varies decidedly from the typical picture

#### REPORT OF CASES IN ONE FAMILY

A member of this family has been under the care of one of us for the last three years The patient, a woman, aged 20, has complained of headaches, irregular menstruation, nervousness and the passing of a very dark colored urine The family history is interesting, in that the grandfather died at the age of 52, from what was thought to have been "heart trouble" He is stated to have had "chronic jaundice" during his entire life

The father of the patient had an attack of jaundice at the age of 12 years, lasting for two weeks Since this attack, he has had an average of two or three attacks of jaundice yearly, usually accompanied by a "cold" At the age of 32, he had an attack of extreme dyspnea, lasting for eight days At that time he entered a hospital in Hamburg, Germany, and during the illness his physicians advised him to have the spleen removed There was a history of yellow sclerae and dark colored urine at frequent intervals since the age of 12 years, also chronic "indigestion" during the major portion of his life This last complaint has been characterized by flatulence and nausea during recent years

There were three brothers in the family, aged 29, 23 and 9 years respectively The eldest brother had an attack of sharp epigastric pain at the age of 19, and entered a hospital where a diagnosis of acute appendicitis was made He refused to be operated on at that time He has had trouble with gas for years, and during the last three or four years he has had pain beneath the right costal margin and low down over the chest on the right side in the region of the lower ribs He states that he has noticed an occasional yellow tint of the sclerae, with the passage of dark colored urine during the last five years He does not remember noticing dark colored urine or yellow sclerae before this time In early adult life he had very frequent and profuse nosebleeds

The second son, aged 23, had "yellow jaundice" at the age of 3 years During the last four years, he has had frequent headaches, and has noticed the passage of dark colored urine for the last six or seven years

The laboratory reports of these patients are as follows

CASE 1—(Father) Wassermann test, negative Fragility test, complete hemolysis 0.23, partial hemolysis, 0.45, hemoglobin, 78 per cent, red blood cells, 4,420,000, white blood cells, 9,600 Differential Polymorphonuclears, 68 per cent, lymphocytes, 20 per cent, polymorphonuclear eosinophils, 4 per cent, large mononuclears and transitionals, 8 per cent, reticulated red cells, 29 per cent

CASE 2—(Eldest son) Hemoglobin, 85 per cent, red blood cells, 4,660,000, white blood cells, 7,600, differential polymorphonuclears, 78 per cent, lymphocytes, 19 per cent, large mononuclears and transitionals, 3 per cent, reticulated reds, 31 per cent The Wassermann test was negative in both antigens Fragility test Complete hemolysis, 0.3, partial hemolysis, 0.45

CASE 3—(Second son) The Wassermann test was negative in both antigens Hemoglobin, 90 per cent, white blood cells, 9,000, red blood cells, 4,880,000, differential polymorphonuclears, 73 per cent, polymorphonuclear basophils, 1 per cent, polymorphonuclear eosinophils, 1 per cent, lymphocytes, 20 per cent, large mononuclears and transitionals, 5 per cent, reticulated reds, 2 per cent Fragility test, normal Platelet count, 188,500

The urine of the father and of the two sons was negative for albumin, sugar and casts, negative for bile, but all three were positive for urobilin, according to Schlessinger's test

At the time these three members of the family were examined, the father had a definite icteric tinge to the sclerae, and the eldest son likewise. In the case of the second son, no definite icteric tinge to the sclerae could be made out. The spleen was palpable, however, in all three.

CASE 4—The third son, aged 9 years, was examined. There was no history of his having jaundice or icteric sclerae, or dark colored urine. His blood findings were normal and the spleen was not palpable.

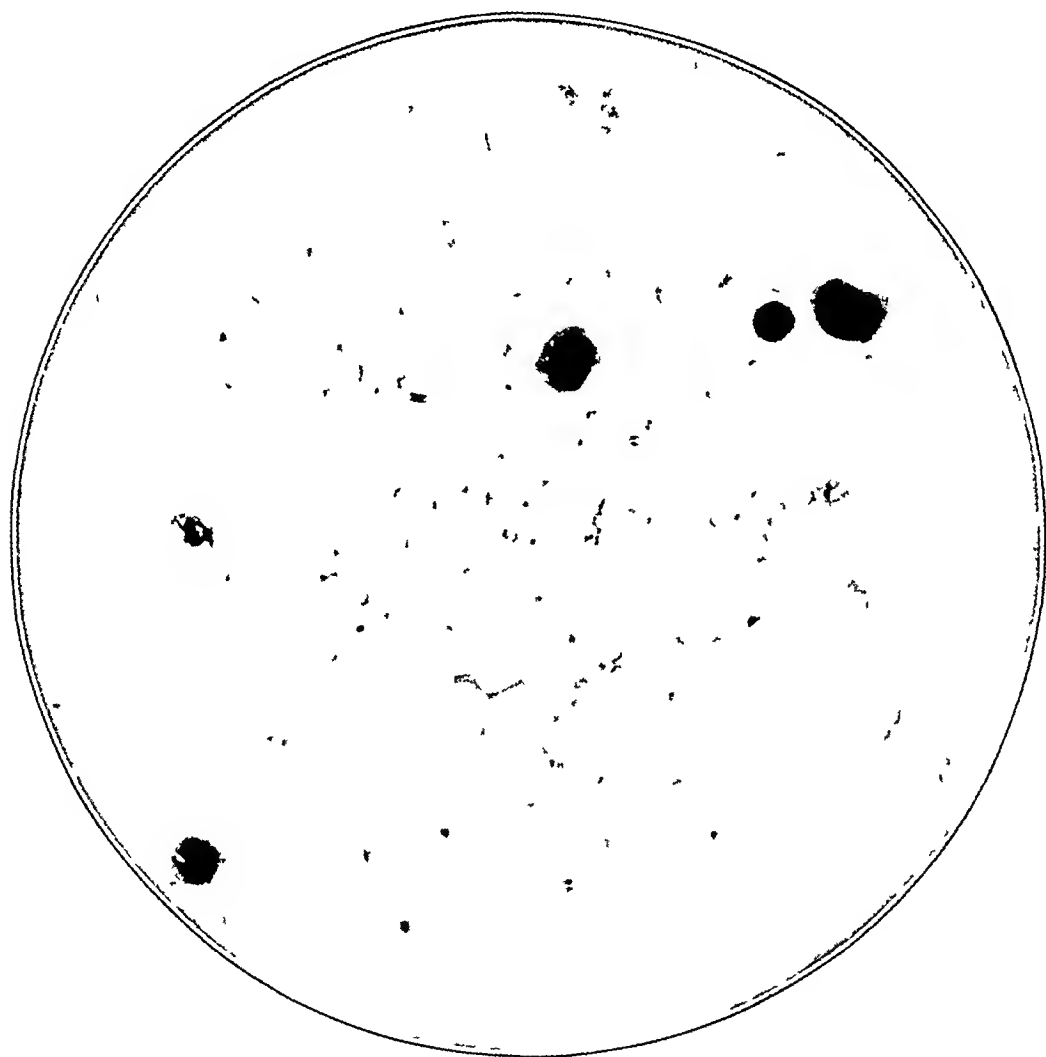


Fig 2—Tibia marrow smear of a patient with congenital hemolytic icterus. Note normoblasts. This marrow approached a true hyperplasia of the red cell elements. Age of the patient, 18 years. Smear obtained before splenectomy.

CASE 5—The daughter, who is the patient under consideration, was born in Germany and came to California at the age of 11 years. She had "yellow jaundice" at the age of 5 years, and was sick for about two and one-half weeks. There is a history of influenza in 1918, but the attack was not severe and there were no complications following. She has had no operations. Catamenia began at the age of 16. There was no irregularity at first and the periods lasted from two to three days, but during the last two years, there has been marked irregularity. When the patient was first seen, the menstrual periods

had nearly ceased and she had gained considerably in weight. Since the age of 5 years, she noticed periods when the urine would be very dark and the sclerae jaundiced. During the last two years, attacks of headaches had been frequent, at times accompanied by dizziness. She also had nosebleeds which at times were quite severe.

Physical examination disclosed an icteric tinge to the sclerae and distended venules over the malar eminences. The skin of the face was very soft and of satin-like quality. There was marked obesity present, with the distribution chiefly over the upper half of the body and about the hips. The heart and lungs were negative. The liver and spleen were both palpable, the spleen being enlarged 5 cm. below the left costal border in the anterior axillary line. This patient's Wassermann test was negative on three or four occasions. The bleeding time was normal and the coagulation time normal. The fragility test was repeated several times and always found to be normal. Blood hemoglobin, 85 per cent. Red blood cells, 4,000,000. White blood cells, 7,000. Differential count: polymorphonuclears, 89 per cent; lymphocytes, 7 per cent; large mononuclears and transitionals, 4 per cent; platelets, 500,000 per cubic millimeter, reticulated red blood cells, 20 per cent. The urine was very dark in color, negative for sugar and albumin, no bile, acetone or urobilin were present. Roentgen-ray examination of the long bones was negative. Skull: the sella was rather small and apparently roofed over, the skull otherwise was negative.

It is felt that this interesting family, undoubtedly, should be classified as a typical congenital hemolytic icterus. The absence of increased fragility of the red cells does not preclude such a diagnosis. None of the members of this family have been much disturbed by their disease with the exception of the daughter, the patient under consideration. None of them have been willing to undergo a splenectomy, and it cannot be said that indications for a splenectomy have been urgent in any members of the family.

#### FAMILY ANEMIAS

We have, in the foregoing, briefly summarized our present knowledge of hemolytic jaundice, for such information leads directly to a consideration of less common familial blood dyscrasias.

Hemolytic jaundice of a severe type may, because of a noncompensating hemopoietic system, exhibit a profound anemia of the pernicious type in the terminal stages. Modern writers acknowledge a type of primary anemia which is characterized by slight icterus, enlarged spleen, evidences of excessive hemolysis and a more or less sluggish response of the marrow. "It would seem that the least compensated cases of the acquired type of hemolytic icterus are, in some way, related to the more chronic hemolytic types of pernicious anemia, and it may at times be difficult to distinguish which condition is present" (Minot<sup>4</sup>).

Weber<sup>5</sup> reports a case of acquired acholuric jaundice with retinal hemorrhages, parathesias and an achlorhydria, the blood picture of which at one time resembled that of pernicious anemia. Weber is con-

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<sup>4</sup> Minot, George R. *Oxford Medicine* 2: 640, 1921, New York, Oxford University Press.

<sup>5</sup> Weber. *Am J M Sc* 138: 24, 1909.

vinced that patients with congenital hemolytic icterus may at times completely lose the jaundice, and have a condition of splenomegalic anemia only, and that in the same family one child may suffer from hemolytic jaundice and another from chronic splenomegalic anemia Hill<sup>6</sup> feels that there is a type of case in which it is impossible to diagnose other than pernicious anemia, but in this the spleen is larger than the ordinary case, pigmentation of the skin more marked and the red blood cells show decreased resistance to hypotonic salt solutions Finally, family icterus and pernicious anemia can exist in different members of the same family as illustrated in Family "B" in a manuscript by Elliot and Kanavel<sup>7</sup> In the fourth generation of this family, one patient died of pernicious anemia, another was intensely anemic and a third suffered from hemolytic jaundice On the other hand, it is impossible to classify certain anemias as acholuric or pernicious as illustrated by Case 8 in a series by Panton, Jones and Riddoch<sup>8</sup> In this type there were prominent characteristics of each disease but the predominance of evidence seemed to favor pernicious anemia The history shows that three members of the mother's family died of a similar type of anemia

It is unnecessary to draw a minute comparison between the two diseases, progressive pernicious anemia being quite dissimilar in regard to its symptoms, prognosis and treatment Both diseases are classified as hemolytic anemias and both show excessive deposits of hemosiderin in the internal organs Both diseases attempt compensation by a hyperplastic hemopoietic system although both the blood and marrow pictures are quite different A family characteristic of pernicious anemia, while rarely seen, does definitely exist as does primary anemia and hemolytic icterus in the same family

We attempt to throw no new light on the causation of pernicious anemia, which still remains a disease of unknown origin, but we do wish to stress an hereditary factor, which manifests itself perhaps as a constitutionally inferior hemopoietic system in some of our obscure essential anemias

#### CASE REPORTS

A constitutional disposition seems to have been a factor in certain cases under review Schmaltz quotes Klein<sup>9</sup> who saw a brother and sister succumb to progressive pernicious anemia Sinkler and Eshner<sup>10</sup>

6 Hill, Lewis W The Resistance of the Red Blood Cells to Hypotonic Salt Solution in the Various Anemias, *Arch Int Med* **16** 814 (Nov) 1915

7 Elliot, Charles A, and Kanavel, Allen B *Surg, Gynec & Obst* **21** 21, 1915

8 Panton, P N, Martland-Jones, A G, Riddoch, G *Lancet* **1** 529 (March 15) 1924

9 Klein, quoted by Schmaltz Nothnagel's Encyclopedia of Practical Medicine on Diseases of Blood, Philadelphia, W B Saunders Company, 1909, p 233

10 Sinkler, W, and Eshner, A A *Am J M Sc* **112** 287, 1896

studied three cases of essential anemia in one family. The father died of pernicious anemia and tabes (probably cold manifestations of the anemia) and the two daughters suffered from severe anemia with low color indexes. Both daughters improved.

Bartlett<sup>11</sup> reports a family of eight, four of whom (father and three sons) died of anemia. Of these, two definitely suffered from pernicious anemia and the other two possibly from the same disease, while a fifth (the daughter) suffered from a prolonged anemia of a chlorotic or secondary type. Patek<sup>12</sup> reports three fatal cases of pernicious anemia (two brothers and a sister) and two other cases of secondary anemia in members of one family. Of other relatives, one paternal cousin suffered from a fatal pernicious anemia and a paternal uncle died of the same disease. Cabot<sup>13</sup> saw two sisters suffer with pernicious anemia, and a brother and sister in another family with the same disease. Roth<sup>14</sup> reports two brothers, both of whom died of pernicious anemia.

Schauman,<sup>15</sup> in reviewing his cases of bothriocephalus infection, came to the conclusion that there is no severe effect on the blood in many who harbor the parasite. However, there were eight families in which two or three members suffered from severe anemia as a result of the common infection. In three other families in which there were two or more cases of anemia, one of the members suffered from pernicious anemia, or chlorosis, while a second suffered from bothriocephalus anemia. Gilbert and Weil<sup>16</sup> report pernicious anemia in two brothers. They quote Potain to the effect that the daughters of chlorotic patients are often chlorotic, and that sons do not escape this predisposition. They further state that the best example of direct heredity is that reported by Rech, who saw four daughters of a chlorotic patient each develop chlorosis at puberty. Recently, DeCastello<sup>17</sup> reported a family of five, in which three sisters died of pernicious anemia and in two of whom necropsy confirmed the diagnosis. An uncle also died of severe anemia which was accompanied by a sore tongue.

We<sup>18</sup> have recently reported, among other cases, that of a woman suffering from a severe anemia, probably of the pernicious type, whose sister died of an intense anemia some years previously. We quite

11 Bartlett, C. J. Family Pernicious Anemia, *J. A. M. A.* **60** 176 (Jan 18) 1913.

12 Patek, Arthur J. Family Pernicious Anemia, *J. A. M. A.* **56** 1315 (May 6) 1911.

13 Cabot, Richard C., in *Osler's Modern Medicine*, Philadelphia, Lea & Febiger, **14** 613, 1908.

14 Roth, O. *Ztschr. f. klin. Med.* **79** 266, 1914.

15 Schauman, Ossian. *Deutsch. med. Wchnschr.* **36** 1218, 1910.

16 Gilbert, A., and Weil, P. E. *Bull. et mem. Soc. med. de hop. de Paris* **3** 543, 1910.

17 DeCastello, Alfred. *Wein. klin. Wchnschr.* **36** 258 (April 9) 1923.

18 Falconer, Ernest H., and Morris, Laird M. *M. Clin. N. A.* **2** 1451, 1923.

recently have studied a patient, a typical case of pernicious anemia, whose mother died of an intense anemia accompanied by a sore tongue. At present we have under supervision a patient with anemia best classified as the pernicious type. This patient, a woman, aged 40 years, said her brother and sister both died of anemia at the ages of 40 and 43, respectively.

Hurst has recently raised the issue as to the constitutional character of achylia gastrica and its relation to the occurrence of familial pernicious anemia. Cases are also reported in which members of the same family suffer from achlorhydria without blood changes, while one or the other parents suffer from pernicious anemia. Such observations lead us away from the field of an inherent abnormality of the hemolytopoietic system.

Poor stock of the predecessors can become dominant during the stress of life of their progeny. An excellent example of poor stock offspring is noted by Willson<sup>19</sup> in a patient who died of pernicious anemia (posterolateral sclerosis and anemia). Of the immediate ancestry, the father died of anemia, the mother was living but suffering from aortic insufficiency and cirrhosis of the liver, an aunt died of typical pernicious anemia and a sister died of a grave anemia. The mother's brother died of mental trouble and the patient's three brothers are invalids, two of whom contracted poliomyelitis with subsequent atrophy of the muscles of the right side and later bladder and renal involvement. One of the brothers suffered from glaucoma, and a third brother from disease of the kidneys. One cannot but feel that in this particular family some inherent quality in the germ plasm is lacking.

#### QUESTIONABLE CASES OF FAMILY ANEMIA

This family consisted of three girls (all dead) from apparently healthy parents who are alive and well at the present time. The mother had two spontaneous miscarriages before the birth of the first living child.

CASE 1—The youngest child, aged 6, contracted diphtheria (cultures confirmed by the S. F. Board of Health) April 12, 1920. Diphtheria antitoxin was administered immediately but the child did not do well for months after. According to the mother's statement, the child never completely recovered, and although up and around and without apparent nerve involvement, became weak, showed a pale yellow color, developed generalized edema, with abdominal distention and died September 10, after an illness of six months. (We have no reports on the condition from which the child suffered other than the mother's statements. She stressed on the child's color, edema, albumin in the urine, and the visiting doctor's statement that the child suffered from anemia. She did not know if the liver and spleen were enlarged.)

CASE 2—The second child, aged 10, was a full term, normally delivered, breast fed baby. Her childhood was not remarkable. She suffered from none of the childhood diseases save chickenpox at the age of 7 years, and had good health until the illness here reported. She entered the University of California

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19 Willson, Robert N. The Spinal Cord in Pernicious Anemia, J. A. M. A. 59 767 (Sept 7) 1912.



Hospital November, 1920, under the care of Dr W P Lucas Her complaint was that of weakness, loss of appetite and anemia following smallpox vaccination in the latter part of October The physical examination showed the following points of interest Patient was small and undernourished with very anemic, somewhat pasty facies, and cyanosis of the lips and extremities The head showed prominent frontal and parietal bosses of old rickets The pupils were regular and reacted to light and in accommodation Ophthalmoscope examination showed the entire fundus and vessels paler than normal with several small patches of exudate in the right background, while in the left there was slight haziness of the nerve head from early edema The nose, ears, teeth and tonsils were in no way pathologic The lymph glands were not enlarged The lungs showed no signs of activity but the roentgen-ray plate gave evidence of peribronchial thickening at the top on the left side The heart was slightly enlarged transversely and downward with a loud systolic murmur at the base and marked pulsation of the vessels of the neck Blood pressure 120 systolic, 85 diastolic The abdomen was protuberant, but the liver, spleen and kidneys were not felt and no fluid was demonstrable The extremities showed no edema The reflexes were equal and hyperactive

Laboratory work showed the following interesting conditions Blood count hemoglobin, 30 per cent, red blood cells, 2,300,000, white blood cells, 7,000, differential polymorphonuclears, 58 per cent, lymphocytes, 28 per cent, large mononuclears, 4 per cent, eosinophils, 2 per cent No blast cells were seen, there was a mild degree of poikilocytosis, a slight anisocytosis, and much acromia, basophilia was marked Blood culture, negative, urine, specific gravity, 1010, there was a heavy trace of alkaline albumin, sugar negative, sediment contained numerous pus cells, no casts or red blood cells were seen The blood Wassermann was negative with two antigens The Pirquet test was negative after twenty-four and forty-eight hours Phenolsulphonaphthalein test was zero at the end of two hours There was marked fixation of the specific gravity with the elimination of salt low and fixed Blood chemistry nonprotein nitrogen, 194 mg per hundred cubic centimeters, urea nitrogen, 152 mg per hundred cubic centimeters, uric acid, 69 mg per hundred cubic centimeters, creatinin, 81 mg per hundred cubic centimeters

A lead test was positive in the stool No lead was recovered from the urine The kidneys were not able to excrete potassium iodid however (see consideration of lead poisoning in the comment)

*Course in Hospital*—The child went steadily down hill for three months and died of a progressive anemia and increasing renal involvement, the course being for the most part afebrile The blood condition was followed intensively throughout The red cells decreased from 2,300,000 on entrance to 1,504,000 terminally The red blood cells ten days before death were 952,000 and the white blood cells on this day were 18,600, with 88 per cent of polymorphonuclear cells The platelets showed a rising curve, the highest count, 968,000, noted when the red blood cells were lowest, 952,000 With the gradual diminution of red cells, a small number of immature forms (normoblasts) appeared in the blood from time to time but vanished entirely five days before death The reticulated cells ranged from 7 to 22 per cent and remained high until death Basophilia, always marked, was much increased for the last ten days The blood chemistry was followed throughout The last few days the urine became smoky, showed acetone and diacetic acid and a fair number of cellular casts The nonprotein nitrogen rose from 162 mg per hundred cubic centimeters on admission to 333 mg per hundred cubic centimeters terminally The blood urea nitrogen rose in the same proportion, 116 mg per hundred cubic centimeters to 287 mg per hundred cubic centimeters terminally Creatinin was 475 mg per hundred cubic centimeters on admission, 109 mg per hundred cubic centimeters terminally Uric acid was 662 mg per hundred cubic centimeters on admission 1135 mg per hundred cubic centimeters terminally The child died in coma The only bleeding noted was confined to the urinary tract

except a slight oozing from the gums. There was no subcutaneous edema. The only therapy other than symptomatic was transfusion of blood, which seemed merely palliative. Permission to perform a necropsy was not granted.

**CASE 3**—The eldest daughter, aged 13, was a patient of Dr. Charles C. Mohun of San Francisco, and by his permission we add this case, which completes the family of three children. Dr. Langly Porter and one of us studied the case during the progress of a severe anemia from which the child suffered. The records are not complete, because the child was confined to her home except during the termination of her illness (two days). There was nothing of importance during the child's infancy which could be interpreted as bearing on the case. The child was full term and normally delivered, bright, got along well at school and was as active at play as other children. She was vaccinated in October, 1920 (the same time as her sister), but she suffered no inconvenience. During the succeeding year, however, the patient began to feel a little below par. A physician advised that the tonsils be removed. This operation was performed in October, 1921, but the child did not improve. There was no suggestion of anemia at this time. In January, 1922, the patient complained of a swelling on the left jaw over the mandible. The nature of this swelling was not determined. The tumor subsided, however, without roentgen-ray treatment or other specific medication. In March the patient experienced a severe attack of influenza from which she never completely recovered. Bronchopneumonia did not complicate the picture, but during her convalescence she began to lose strength, tired easily and became pale. She was unable to remain up and remained in bed again about a month after the before mentioned illness. This ushered in her terminal malady, a profound anemia, the nature of which was never determined. The condition of the blood simulated closely that of her sister, described in the foregoing. The kidneys, however, seemed in no way involved.

*Physical Examination*—When seen by one of us the child was mentally clear, confined to her bed and showed a profound pallor. The sclerae were mildly icteric, the pupils were regular and reacted to light, the backgrounds were pale, no exudate or swelling of either nerve head was noted. Ears and nose were normal. The mouth showed no stomatitis. The tonsillar fossae were clear. The vessels pulsated in the neck, the thyroid was palpable, especially the isthmus. There was no increased adenopathy in the neck or other gland groups. The breasts were undeveloped for a girl aged 13, there was no pubic or axillary hair. The lungs were clear. The heart was rapid but not enlarged. A loud systolic murmur was heard best at the base and a hum was noted over the vessels of the neck. There was no diastolic murmur heard over any of the valve areas. The pulses were equal, regular, of small volume and rapid. Blood pressure 105 systolic, 75 diastolic. The liver and spleen were not felt, no masses were noted in the abdomen. The extremities were negative. The reflexes were equal.

*Clinical Pathology*—Blood hemoglobin, 20 per cent, red blood cells, 2,300,000, white blood cells, 8,000, polymorphonuclears, 82 per cent, lymphocytes, 16 per cent, large mononuclears, 2 per cent, eosinophils, 0. Marked achromia was present and a mild degree of antisicytosis and poikilocytosis. No tailed cells were seen, an occasional stippled cell was noted. Reticulated cells, 11 per cent, two normoblasts were seen. Urine acid, specific gravity, 1.018, albumin was negative, sugar negative, sediment negative, there was a slight trace of urobilin, stool was negative for ova. Blood culture was not done. A blood Wassermann test was not made. A second blood count, three days after the foregoing, showed an increasing anemia. Hemoglobin, 20 per cent, red blood cells, 1,800,000, white blood cells, 5,600, polymorphonuclears, 72 per cent, lymphocytes, 22 per cent, large mononuclears, 3 per cent, eosinophils, 1 per cent, basophils, 0, blood platelets, 260,000 (Wright and Kinnicutt method), reticulated cells, 9 per cent. No normoblasts were seen, there was much central pallor of the red cells which seemed otherwise to be normal.

Course Afebrile The child progressed rapidly downward, and with no signs of bleeding from the mucous membranes or into the skin, developed an acute left hemiplegia, and died a week after the last noted blood count. It was impossible under existing conditions to study the child further.<sup>20</sup> Permission to perform a necropsy was not obtained.

Unfortunately, little conclusive evidence can be drawn from the study of these three cases. We assume the first child died of nephritis as did the second, the time interval between the deaths of the two children being close enough to excite interest in some common toxic factor. Investigation proved that the children were exposed to lead in a newly painted house a few months before the death of the first child. The positive lead test in the stool of Case 2 added some evidence to lead as a common etiologic factor. Against this, however, is the fact that Case 2 at no time presented a lead line, nerve palsies or colic. It is felt that lead intoxication, sufficient to give evidences of kidney and blood damage to the extent that they were found in the patient, should have given other evidences of lead poisoning. It is further problematic just how much reliance can be given to a positive lead test after potassium iodid in a child living in a commercial district of a large city. While lead intoxication, however, was given consideration after the death of the second child, such intoxication was challenged when, after a period of one and one-half years, the third child developed what appeared to be a severe hemolytic anemia without kidney involvement and died with a profound blood dyscrasia, the cause of which was not determined. We hesitate to make any positive statements and we grant the incompleteness of our records. We have grouped the cases in this paper for consideration only.

#### REPORT OF CASE

Mrs. J. S., aged 41, gave a history of having periods of anemia ever since about the age of 13. She stated that, as a young girl, she was frequently taken to different physicians, who always found her anemic, and invariably prescribed some form of iron. At length it was felt scarcely necessary to consult a physician about her malady. When weakness manifested itself and an approaching lassitude, she would go to a drug store and purchase the tonic. After a few weeks of iron medication, the symptoms would disappear and she would feel quite normal for perhaps four, five or six months, and sometimes for a year when the symptoms would again recur. Periods as long as two years occurred when (to use her own phrase) "her blood would stay up and she would feel normal."

The patient's blood count had always shown a moderate secondary anemia with central pallor, but otherwise a negative appearance of the red cells and a rather low hemoglobin. The white count has always been normal, and a study of the blood smears and of the blood counts, when the patient felt weak and run down, showed a blood picture suggestive of the chlorotic type of anemia. It was felt from the history, especially as this patient dated the onset of her anemia to about the time of puberty, that we were dealing with chlorosis.

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20 Recently both parents were questioned regarding any of their immediate family or their parents who suffered from any blood disease. The information received was entirely in the negative.

A sister of the patient's mother has likewise been anemic since childhood, has had to take frequent courses of iron by mouth and also iron injections. The patient's mother has also been anemic, at intervals, for years and her anemia always responds to iron medication, according to a statement of the patient.

We have no data as to the type of anemia present in the mother and in the mother's sister, but as the patient is a very intelligent woman, we have accepted her statement that the mother and aunt have suffered from anemia during the major portion of their lives.

#### HEMOPHILIA, IDIOPATHIC PURPURA HEMORRHAGICA, AND FAMILIAL MULTIPLE TELANGIECTASES

In hemophilia we find a perfect illustration of an inherited sex-linked recessive unit character, limited to males and transmitted only by the opposite sex. The underlying disturbance is an abnormality of the blood or blood forming organs, characterized by a deficiency of prothrombin, an essential element in normal coagulation. The number of platelets in the circulating blood are not diminished, the bleeding time is normal but the coagulation time is much prolonged. The outstanding features are a liability to hemorrhage, most commonly into joints and from the nose or insignificant cuts and bruises, less commonly from the kidneys and bowel. Surgical procedure is often followed by fatal bleeding.

Idiopathic purpura hemorrhagica is quite dissimilar. The thrombopenia, characterized by platelet deficiency, is an essential characteristic. The phenomena which depend on this deficiency are prolongation of the bleeding time and a soft, nonretractile blood clot. The condition occurs in both sexes and is characterized by purpuric skin blotches, petechiae and hemorrhages from the mucous membrane. Familial tendencies have been used as a point against the disease. Christian<sup>21</sup> states, however, that occasionally purpura hemorrhagica is hereditary. Cousin<sup>22</sup> describes a family in which the disease occurred in three different branches, and Rosenfeld<sup>23</sup> cites two cases of idiopathic purpura in brothers. He further brings up the question whether in these families there is an inherent weakness of the germ plasm, which makes itself manifest in a deficiency of blood platelet formation or in a primary vascular degeneration or both. Most writers admit, in addition to platelet deficiency, a vascular degeneration.

It needs but brief mention here to recall a familial type of recurring epistaxis associated with multiple telangiectases of the skin and mucous membranes which, if bleeding is allowed to continue, produce grave secondary anemia. The family character of the disease was put on a

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21 Christian, Henry A. *Oxford Medicine* 2:784, 1921, New York, Oxford University Press.

22 Cousin, M. *Ann de med et chir inf* 17:633, 1913.

23 Rosenfeld, Arthur S. *Idiopathic Purpura with Unusual Features*, *Arch Int Med* 27:465 (April) 1921.

firm clinical basis by Osler <sup>24</sup> and much literature has accumulated since. The condition is local, and consists of multiple punctiform angiomas of the skin and mucous membranes of the nose, lips, cheeks and tongue. It has nothing to do with hemophilia or purpura. We have recently studied the tibia marrow of a woman who suffered from this disease. So far as could be ascertained, the marrow specimens obtained by puncture were normal as to cellular content. The puncture was done during a period when no bleeding was experienced and the hemoglobin, red and white blood counts were normal.

One of us has recently seen, with Dr. Langly Porter, a case which can best be classified, from our observation, as idiopathic purpura and in which an hereditary tendency is suggestive.

The patient, P. G., aged 7, an only child, developed normally throughout infancy without any serious disturbance in health. The tonsils were removed about two years before this illness, without an abnormal amount of bleeding. Within the last year the mother noted that the child's shins were "black and blue" frequently, a condition which was attributed to trauma induced by vigorous play with other children. In the summer of 1923, however, while on a summer vacation in Canada, large purpuric blotches were noted on the skin of the buttocks, back and legs. Petechiae also were numerous on the extremities. There was no preceding illness to account for such a condition. No bleeding from the mucous membranes was noted. Dr. Porter saw the child at the height of the disease. The technician stated that the platelet count was but 10,000. Study of smear preparations, which one of us examined, showed a total absence of blood plates. A systematic examination of the blood condition was begun about two weeks after the more acute condition subsided. There were still seen fading purpuric spots on the back and legs, with a few petechiae noted on the buttocks. The laboratory work showed the following: hemoglobin, 80 per cent; red blood cells, 4,520,000; white blood cells, 7,000; differential count: polymorphonuclears, 58.5 per cent; lymphocytes, 31.5 per cent; large mononuclears, 8.5 per cent; polymorphonuclear eosinophils, 2.5 per cent; platelets, 110,000; reticulated red cells, 2 per cent. Bleeding time, twenty-five minutes; coagulation time, ten minutes in an 0.9 cm. tube. Clot nonretractile in character. Prothrombin time, ten minutes; control time, six minutes.

From both the clinical and laboratory side, the child belongs in the class of idiopathic purpura. The family history, however, is somewhat suggestive of an hereditary factor and is thus quoted in some detail. The mother of patient, Mrs. G., has always bruised very easily. On several occasions she complained of severe neuralgia in the region of the eye which subsequently turned "black and blue." She also has noted little red spots similar to those seen on her son which have variously appeared on different parts of her body (petechiae?). Some years ago she bled on several occasions from small hemorrhages which came from the lungs proper (a physician at this time found active tubercular infection). Her menstrual function is not disturbed. Mrs. G.'s half sister always bruised and bled easily. The latter was operated on in England for a gallbladder condition from which she died. She was given many preparatory injections however, before the operation, which were directed toward her bleeding tendency (Mrs. G.'s statement). Mrs. G.'s niece (a daughter of the before mentioned half sister) has always suffered from violent nose bleeds and purpuric spots. A week after an operation on the antrum, the girl bled intermittently throughout the entire day and caused the surgeon much alarm. Mrs. G. has two other sisters who do not suffer from bleeding. The

mother died at the age of 62 from diabetes, and of her two husbands, the first died of hemorrhage from the lungs after exertion (probably tuberculosis), the second died of a hemorrhage into the brain at the age of 54

#### SICKLE CELL ANEMIA

Sickle cell anemia is a rare disease and so far as known is confined to the negro race. The disease is hereditary, and occurs in and is transmitted by both male and female, according to the mendelian law. The erythrocytes show crescentic and sickle shapes in the wet preparations, these bizarre forms increasing markedly at the end of twenty-four hours in the wet sealed preparation. There may be a mild to a severe anemia with a slight increase in white cells and blood plates. The blood dyscrasia is commonly accompanied by chronic leg ulcers. Huck,<sup>25</sup> in an excellent recent article, reports the genealogical tree of families studied at Johns Hopkins Hospital. He concludes, among other facts, that the sickling of the red blood cells is due to some factor inherent to the cells and not to any substance in the serum. We have had no experience with the disease.

#### THE LEUKEMIAS

Ward<sup>26</sup> has compiled statistics which tend to disprove the infective theory of acute leukemia. After a review of more than a thousand cases it might be advisable to quote certain of his conclusions: (1) "That there is a congenital form of leukemia which occurs in children whose parents are not leukemic." (2) That leukemic parents have never been known to transmit the disease to the new-born child."

McGavran<sup>27</sup> recently reported three cases of leukemia in one family and reviews other instances. In the family reported, one brother died of the myeloid type, another of the lymphoid variety, while the uncle (father's brother) died of the same disease. McGavran does not wish to be understood as trying to strengthen the claim of heredity as a factor in this disease, nor do we. If the leukemias are proved to fall into the malignant class, however, an inherited recessive character as has recently been suggested for cancer, might be given consideration.

#### REPORT OF CASE

The case here reported, one of chronic myeloid leukemia, has been followed for over three years in the University of California outpatient department. The disease of the patient is typical enough, presenting an enlarged spleen, bleeding gums, anemia, platelet increase, marked myelocytosis and a white count which has varied from 20,000 to 400,000 under the influence of roentgen-ray therapy. The family history, however, is considered of sufficient interest to report in more detail. The patient's mother suffered from diabetes. Of the mother's nine sisters, two died in infancy, cause unknown, and five died

25 Huck, John G. Bull. Johns Hopkins Hosp. **34** 335 (Oct.) 1923

26 Ward, Gordon. Brit. J. Child Dis. **14** 10 (Jan.) 1917

27 McGavran, Charles W. Am. J. M. Sc. **164** 545, 1922

of diabetes. The patient describes her aunts as stout but growing thin and wasting away. They all had sugar in the urine. One of the aunts gave birth to a son who was born with a large spleen (mother's report). The boy was always delicate and anemic. He died at the age of 36 with an abscess on the spleen (?). The spleen was enlarged throughout life. Of the patient's five brothers and sisters, one brother has recently died of diabetes and one of heart disease. There are three sisters who thus far are well. The patient's only child has suffered all her life from asthma.

GAUCHER'S DISEASE    SPLENIC ANEMIA    UNCLASSIFIED  
SPLENOMEGALY

The family character of Gaucher's splenomegaly is fairly well established. It seems to be a one generation disease, for there is no evidence of transmission from parent to child. The disease ordinarily makes itself manifest in childhood and may affect several members of the same family, with a high incidence in the female sex. The course is decidedly chronic with little disturbance of health until late in the disease.

The features which characterize the condition are enormous splenomegaly, moderate liver enlargement, pigmentary skin changes of the face, neck and hands and a peculiar wedge shaped thickening of the conjunctiva on either side of the cornea. No lymphadenopathy, jaundice or acites are observed. There is a tendency to bleed from the gums and nose but with the exception of a moderate leukopenia, the constituents of the blood are not decreased until late in the course, when anemia becomes a part of the picture. The histopathologic picture shows large multinucleated phagocytic cells (Gaucher's cells) in the spleen, liver, lymph glands and bone marrow (reticulo-endothelial system). These large cells are probably modified reticular cells although their origin is still much disputed.

Banti's splenomegaly must be sharply differentiated. Familial occurrence is a decided rarity, although a family of three children is described by Foote<sup>28</sup> as suffering from the condition. One of the children died of pneumonia and the organs were obtained for necropsy purposes.

The symptom complex consists of a large splenic tumor, recurrent attacks of hematemesis, moderate anemia, with a constant leukopenia. The late stage with hepatic cirrhosis is an added feature. Extirpation of the spleen ameliorates the condition if liver changes are not far advanced.

The pathologic condition is quite characteristic. The enlarged spleen is often held by firm adhesions to the neighboring structures, in which huge collateral blood channels course, while the main splenic veins are enormously enlarged. In microscopic section there is moderate atrophy of the malpighian bodies and few of the pulp cells. There is a marked

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28 Foote, John. *Internat Clinics* 2 52, 1919

reaction of the intrasplenic fibrous tissue. The liver, in many cases, shows cirrhotic changes at times to an advanced degree.

We have studied rather intensively over a period of a year, a condition of familial splenomegaly with blood changes in two brothers (Mexicans). Our efforts at placing these children in any known class of disease have not been attended by any success. They apparently do not suffer from their malady at present and scarcely understand why they are returned periodically for study.

We are much interested in the report of DeLange and Schippers<sup>29</sup> on familial splenomegaly, seven children of which suffered from enlarged spleens while the parents and grandparents were normal. One child, probably two, have fallen victims to the disease and the eldest of the two girls has begun to show signs of cachexia. A splenectomy was performed on the youngest and on the second child. Sections of the tissue showed no pathologic reaction in the spleen and lymph glands. Hypertrophy was the only finding. The authors conclude "Apparently have to deal with a congenital vitium primae formationis, on account of which the spleen has developed into a state of giant growth." They further feel that in the foregoing cases they are dealing with a familial progressive cachexia, in the course of which a hemorrhagic diathesis occurs antemortem.

It is unfortunate that the family with hereditary splenomegaly which Wilson<sup>30</sup> and Wilson and Stanley<sup>31</sup> report (1890-1893) could not have been studied by more modern methods. The cases probably fall into the hemolytic jaundice group.

Bastai<sup>32</sup> observed three cases of splenomegaly with cirrhosis of the liver in two sisters and a brother, with a symptomatology resembling Banti's disease. The histologic picture, however, in every case, showed no true process of adenofibrosis of the splenic pulp. The writer considered that the disease as studied could not be identified with any well established nosographic unity (original article not obtained). Pantaloni<sup>33</sup> under the title "Is Banti's Disease Familial?" described two sisters with Banti's disease, one case proved by section after splenectomy and the other presenting signs of splenomegaly and anemia with subsequent signs of hepatic cirrhosis and ascites. The writer believes that in these two patients there existed a special constitutional organic predisposition especially on the part of the spleen, a predisposition which would have rendered possible the growth in that

29 DeLange, Cornelia, and Schippers, J. C. Familial Splenomegaly, *Am J Dis Child* **15** 249 (April) 1918.

30 Wilson, Claude. *Tr Clin Soc London* **23** 162, 1890.

31 Wilson, C., and Stanley, D. *Tr Clin Soc London* **26** 163, 1893.

32 Bastai, Pio. *Internat M & S Survey* **4** 583, 1922.

33 Pantaloni, Pio. *Internat M & S Survey* **4** 584, 1922.



organ of those microbes capable of determining the splenic alterations which characterize Banti's syndrome (original article not obtained)

From this meager review of the literature it is quite obvious that familial splenomegalies may fall into quite different groups. We therefore present these cases for consideration<sup>34</sup>

#### REPORT OF CASES

CASE 1—J S, a boy, aged 12 years, of Spanish descent, entered the U C Hospital in January, 1922. The boy was sent in for study because a large spleen was found during the course of a routine physical examination for entry at the San Francisco nursery. The child spoke broken English, having lived in Mexico City for eleven years. The following information was obtained from the guardian, which is meager at best. The father, a seafaring man, is alive and so far as known, is well. We have had no opportunity to converse with or examine him. The child's mother died at the age of 35, from cancer of the uterus. There is but one other child in the family, a younger brother who is well but who, on examination, presented an enlarged spleen.

The patient has been comparatively well during childhood, with the exception of an attack of dysentery from which he suffered two years ago. This consisted of from ten to twelve stools daily, full of blood and mucus, which condition lasted for about two months. There was a very questionable history of malaria given. A history of slight bleeding from the gums during the last two years was the only other inconvenience suffered.

The major points in the physical examination were as follows. The skin was brown (racial), rough and dry with many small nevae. The pupils were regular and reacted to light. The conjunctiva was not pale and the sclerae showed no evidence of jaundice or other abnormalities. The backgrounds were negative. The gums were red and spongy and bled easily when irritated. The tonsils were markedly hypertrophied. There was a slight enlargement of the anterior, posterior and submaxillary cervical glands but no involvement of other glandular groups. The lungs, heart and arterial system were not remarkable. The spleen was markedly enlarged and hard, its tip extending 9 cm below the costal margin. The liver was not felt and there were no other abnormalities noted in the abdomen. There was a marked right scoliosis. The genitalia and extremities showed no abnormalities, and both the skin and tendon reflexes were equal.

*Clinical Pathology*—The urine was negative. The Pirquet test was negative. The blood Wassermann test was negative. Bile was not present in blood plasma. Clotting time, two and one-quarter minutes. Fragility of the red cells was noted. Hemolysis began at 0.46, complete at 0.34 per cent, sodium chlorid solution. Blood count: red blood cells, 4,736,000, white blood cells, 5,200, differential count: polymorphonuclears, 58 per cent, hemoglobin, 80 per cent, lymphocytes, 30 per cent, large mononuclears, 9 per cent, polymorphonuclear eosinophils, 3 per cent. No malaria organisms or crescents were found. Blood count (three day interval): red blood cells, 4,270,000, white blood cells, 7,500. Differential count: polymorphonuclears, 52 per cent, polymorphonuclear eosinophils, 13 per cent, lymphocytes, 27 per cent, large mononuclears, 6 per cent, myelocytes, 2 per cent. Marrow puncture (tibia). Hypertrophic marrow, both red and white celled elements being conspicuous.

The patient reentered the hospital August, 1922, for study. As previously, the gums were spongy and bled easily. The tonsils were greatly enlarged and the submandibular nodes had not receded in size. The spleen was somewhat larger,

34 From the pediatric wards of Dr W P Lucas

extending 11 cm from the costal margin. The liver edge was questionably palpable. There was no free fluid in the abdomen. A mild degree of anemia had developed, with a definite change in the differential count. Thus hemoglobin, 75 per cent, red blood cells, 3,360,000, white blood cells, 8,200. Differential count: polymorphonuclears, 55 per cent, lymphocytes, 18 per cent, large mononuclears, 27 per cent.

Of these large mononuclear cells, over 50 per cent showed an irregular lobated nucleus with a finely granular cytoplasm.

Stool. Cysts of *ameba histolytica* were found.

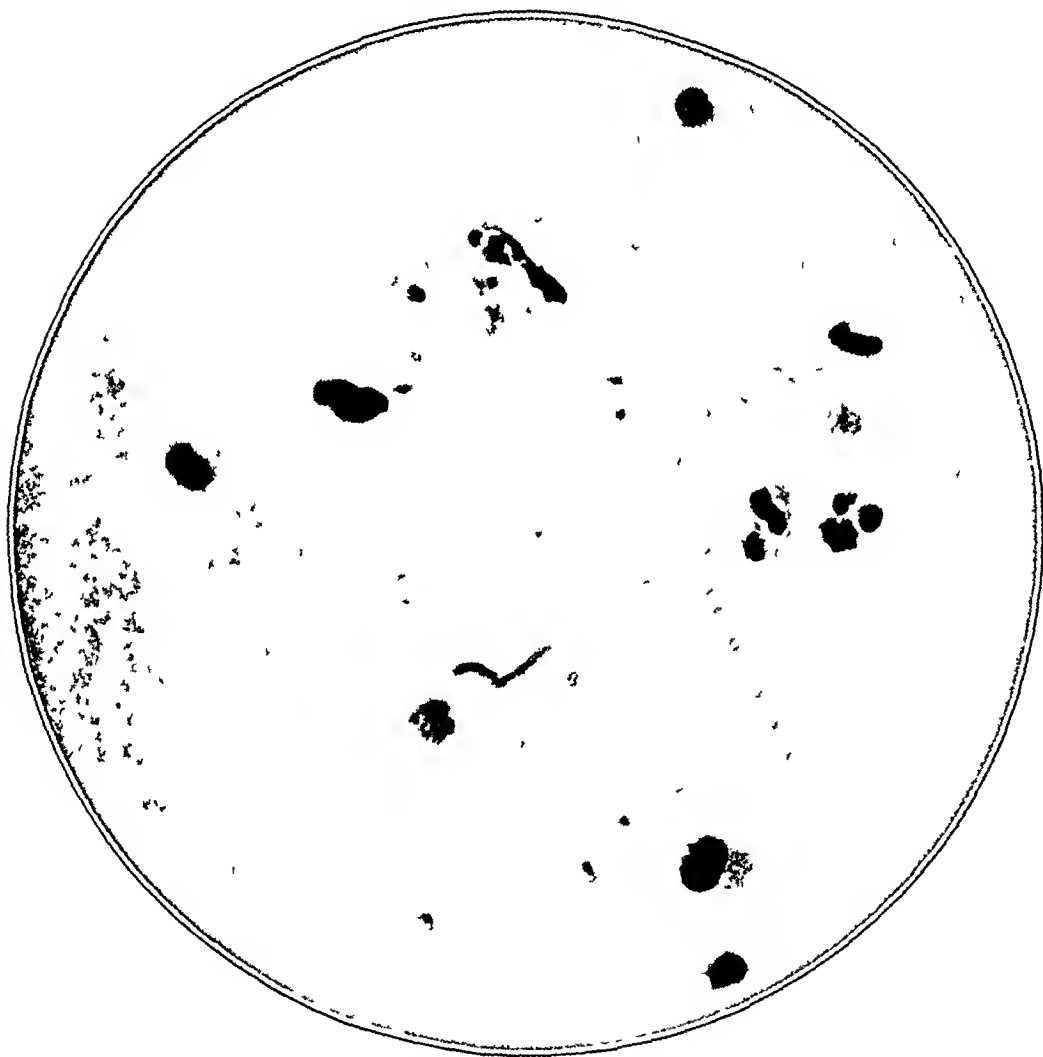


Fig 3—Tibia marrow smear of R S, aged 6 years. The smear shows a definite hyperplasia but to a lesser degree than his older brother.

Bone marrow puncture (opposite tibia) showed the same diffuse hyperplasia of the erythroblastic and leukoblastic elements as did the previous specimen from the other leg.

CASE 2—At this time the brother, R S, aged 6 years, was admitted for study. There was nothing of importance in his former history; he had been healthy, and developed the same as other children. He had lived with his brother in Mexico but had not suffered from dysentery or malaria. His physical examination revealed little save a mild gingivitis and a definitely enlarged spleen which was hard, notched and extended 6.5 cm below the costal margin. The liver was not felt and no free fluid was noted in the abdomen.

*Clinical Pathology*—The urine, Pirquet and Wassermann tests were negative. Blood examination hemoglobin, 85 per cent, red blood cells, 4,700,000, white blood cells, 4,800. Differential count polymorphonuclears, 60 per cent, lymphocytes, 30 per cent, large mononuclears, 10 per cent. No plasmodia were seen. Clotting time, three and one-half minutes. Bleeding time, three minutes. Platelets, 224,000. Fragility commenced at 0.45 per cent, complete at 35 per cent, sodium chlorid solution. Blood urea nitrogen 16 mg per hundred cubic centimeters, nonprotein nitrogen, 31 mg per hundred cubic centimeters, creatinin, 2.2 mg per hundred cubic centimeters, uric acid, 3.5 mg per hundred cubic centimeters.

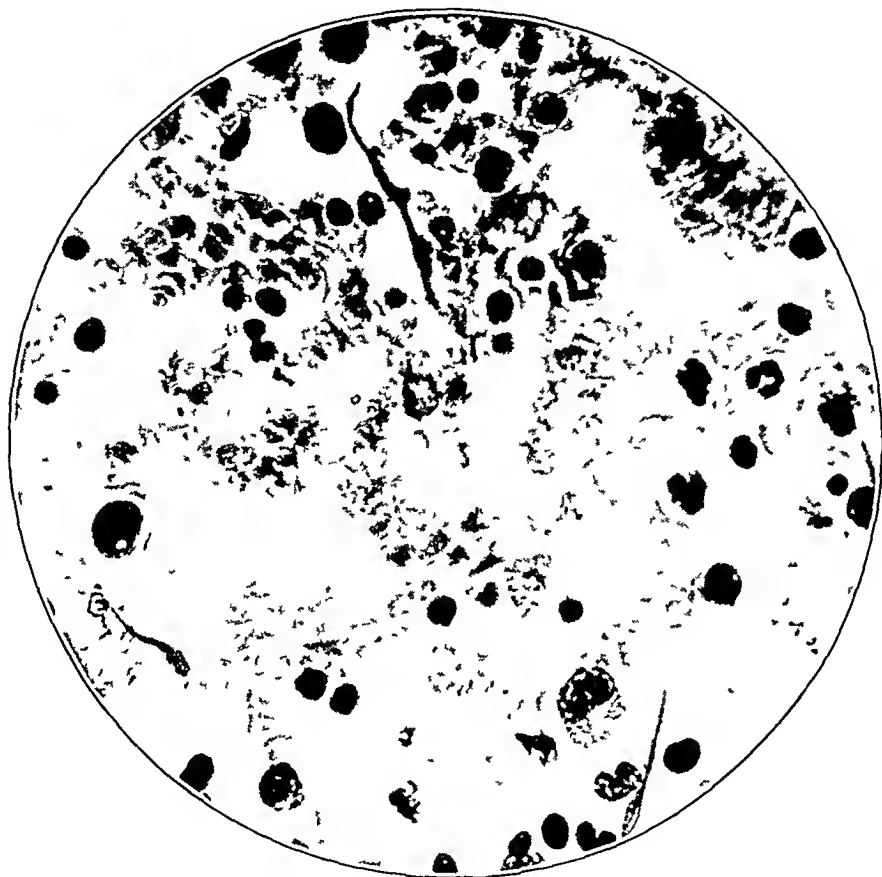


Fig 4—Tibia marrow smear of J S, aged 12 years. Note hyperplasia of both white and red cell elements.

*Stool* Giardia cysts were found.

*Tibia marrow puncture* The smears showed a definite hyperplasia, not to the extent of the older brother however and with the white cell elements less prominent. No plasmodia were seen in the marrow smears.

#### COMMENT

It is difficult to classify these brothers. We feel that the parasites found in the stool do not aid in a solution of the problem. The cases do not fit clinically into a type of Gaucher's disease or Banti's syndrome and so far as known into no common infectious group. Thus far our most helpful information is a known pathologic long bone

marrow which is in keeping with the abnormal blood picture we studied. It might seem that the bone marrow of the elder brother suggests the hyperplasia of myeloid leukemia. The uniformity of the leukoblastic elements in no way compares to the tibia marrow of Mrs. H., a typical case of myeloid leukemia. Furthermore, the larger type of cell seen is not comparable to the Gaucher cell of that disease. We feel that there is not sufficient enlargement of the lymph glands to offer much constructive data from sections of the same. Splenic puncture (besides its dangers) offers very little, but sections from the spleen might well clear the whole condition from a diagnostic point of view. So far we have found no indication for splenectomy.

#### CONCLUSIONS

1 Before cases are grouped as familial splenomegalies, it is necessary to eliminate certain common sources of infection, syphilis, malaria and certain of the tropical diseases being most common factors for error.

2 Before cases are grouped as familial anemias, it is necessary to eliminate certain common toxic and infectious factors, lead arsenic, syphilis and malaria being common sources of error.

3 Family diseases of the spleen are probably related in many instances to a congenital predisposition of the hemolytopoietic system.

4 A disposition toward inferiority of the hemopoietic system probably exists. Detailed family histories are essential to prove this point.

# A CASE OF SICKLE CELL ANEMIA WITH NECROPSY \*

GEORGE S GRAHAM, M D

BIRMINGHAM, ALA

Sickle cell anemia is a new disease, in the sense that it is just coming into general attention. It appears to be a familial disease or status peculiar to the negro race. Chief of its characteristics is an anomaly of the red blood cells evidenced in their tendency to assume elongated sickle or crescent shapes or various bizarre distortions. In some cases the disease appears to consist in nothing more than this erythrocytic abnormality, again, certain minor physical disabilities may be added, while in occasional cases there are recurrent paroxysms of acute illness with fever, prostration, pain in the extremities or joints and evidences of marked hemolytic blood destruction.

## HISTORICAL DATA

First recognition of the disease is credited to Herrick<sup>1</sup> who, in 1910, described a case of severe anemia in which he had noticed that many of the red corpuscles were of peculiar elongated sickle shaped or crescent shaped forms. Washburn<sup>2</sup> described a similar case from Virginia in the following year. The third case was reported from St. Louis in 1915 by Cook and Meyer<sup>3</sup>. Mason<sup>4</sup> described a fourth case in 1922. Two illuminating papers appeared in August, 1923. Sydenstricker, Mulherin and Houseal<sup>5</sup> described two cases in detail and reported collateral study on twelve relatives, nine of whom were found to show evidences of the disease. They supplemented their clinical observation by reporting the necropsy findings in one of their patients. This is the first necropsy study on record. Two months later, Huck<sup>6</sup> published a careful clinical and laboratory study of two cases and added observations on a third practically symptomless case. He discovered a more or less

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\* From the department of pathology, Graduate School of Medicine of the University of Alabama.

1 Herrick, James B. Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, *Arch Int Med* **6** 517 (Nov.) 1910.

2 Washburn, R. E. Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, *Virginia Med* **15** 490, 1911.

3 Cook, Jerome E., and Meyer, Jerome. Severe Anemia with Remarkable Elongated and Sickle-Shaped Red Blood Cells and Chronic Leg Ulcer, *Arch Int Med* **16** 644 (Oct.) 1915.

4 Mason, V. R. Sickle Cell Anemia, *J. A. M. A.* **79** 1318 (Oct. 17) 1922.

5 Sydenstricker, V. P., Mulherin, W. A., and Houseal, R. W. Sickle Cell Anemia, *Am J Dis Child* **26** 132 (Aug.) 1923.

6 Huck, J. G. Sickle Cell Anemia, *Bull Johns Hopkins Hosp* **34** 335 (Oct.) 1923.

incomplete syndrome in eleven other persons, all but one of whom were found through systematic examination of the blood in relatives of the three original patients. Finally, Sydenstricker<sup>7</sup> summarized present knowledge of the disease and reported a second necropsy.

#### FREQUENCY

Both Huck and Sydenstricker state that the disease is relatively common. The former<sup>6</sup> reported that in November 1923, forty cases had been seen and studied at Baltimore. The latter<sup>7</sup> found forty cases in his Augusta clinic during a period of sixteen months, and estimated that the disease occurred in about 0.2 of 1.0 per cent of all negroes examined in the clinic. A word of explanation should be added, however. As already noted, the disease appears to exist in widely varying degrees of severity. In some persons it may present nothing more than an anomaly of the red corpuscles, demonstrable only after examination by a method seldom or never used in routine blood study. In other cases there are minor complaints that would be without significance unless one were on the lookout for the disease. In a few cases the patient is subject to periodic attacks of more or less complete physical disability. The actual number of reported cases in which the subject was sufficiently ill to seek medical assistance can still be counted on the fingers. Thus, of the fourteen cases reported by Huck, only two were actually incapacitated. Three others showed pronounced anemia with partial or severe disability, four had only minor complaints and six had never shown any symptoms. The detailed report of Sydenstricker's cases has not yet appeared, so that the actual morbidity among them cannot be determined. As the disease becomes better understood, it will be necessary to evaluate the importance that is to be placed on the mere fact that the blood of a given person contains anomalous red corpuscles.

So far as can be determined from the papers thus far published, detailed study has been made only in the first four cases reported and in two of Huck's and two of Sydenstricker's—a total of eight cases. Three necropsies have been performed. Sydenstricker reports two of these, one in a child and one in a man, aged 62, without active symptoms. The third necropsy is referred to briefly by Huck. In Huck's case the records are incomplete, while in Sydenstricker's second case, only a summary of the findings is given. In view of these facts, it seems worth while to report a single case of the disease in which clinical study was followed by postmortem examination.

#### CASE REPORT

E. A., a man, negro, aged 30, was admitted to the Hillman Hospital, March 14, 1924. His physician had made a diagnosis of acute meningitis.

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<sup>7</sup> Sydenstricker, V. P. Sickle Cell Anemia, Southern M. J. **17** 177 (March) 1924.

*Family History*—The patient's mother had died of pneumonia at the age of 32. The preceding condition of her health is not known. The father was about 75 years old and able to do light work. Two brothers and three sisters died in infancy or childhood, cause unknown. Three sisters and one brother are living. The sisters are well. The brother was aged 24, looked well but had always tired easily and was not able to do hard work. He had attacks similar to those of the patient but they were not so severe. They were especially liable to come on after fatigue or chilling. He has had a lesion "like a burned place" on the ankle for the last ten years. The patient knew of no other member of his family similarly affected. The only relative accessible to us was a sister who came to the hospital after the patient died. She was aged 27, well nourished, the mother of five children all of whom were said to be well. Her blood picture was normal, there was no scleral discoloration and no sickling of her corpuscles could be determined.

*Personal History*—The history was vague, owing to the patient's low mentality. Whooping cough was the only childhood disease remembered. Venereal disease was denied. The patient never considered himself unhealthy but admitted that he had never been able to do heavy work. By occupation he was a bootblack. Since the age of 8 or 9 years he suffered from recurrent attacks of illness with pain in extremities or joints. The particular joints affected varied from time to time. At first the attacks recurred at intervals of a few weeks or months but gradually became less frequent. The last occurred about a year previous to admittance to hospital. His appetite was fair except during attacks, when he had no desire for food, and eating was often followed by epigastric pain. During attacks the urine was "red." In free intervals it was colorless. The patient always tired easily, became dizzy and short of breath on slight exertion. He has had an ulcer on the left shin for about fifteen years. An unsuccessful attempt at surgical cure was made in a hospital about three years ago. Appendectomy was performed at the same time.

*Present Illness*—The patient dated his illness from exposure during a snow storm about one week before, when he got cold and wet. Following this, the appetite failed, he became weak and had much epigastric pain. On the day of admission he developed severe pain in back of head and neck with stiffness and soreness of the posterior cervical muscles. There was also severe pain in the back. The attack was similar to ones from which he had previously suffered.

*Physical Examination*—The patient was well nourished. Temperature, 101 F., pulse, 102, respiration, 22. The head was slightly retracted, there was moderate resistance to flexion on trunk. Stated age was 30 years but he looked nearer 18 years. The pupils reacted to light and in accommodation. The sclerae showed a slight greenish color and the skin was suggestive of icterus. The gums were bluish and pale. The tonsils were atrophic and adherent. The anterior cervical glands were not palpable. There were a few soft enlarged glands in the posterior cervical triangle, more on the right than on the left side. The chest was well formed. The lungs were negative except for a few transitory rales at the left base. The heart was slightly enlarged, the sounds clear with no murmurs. The abdomen was slightly distended, there were no masses nor rigidity, but a slight generalized tenderness. The liver was not enlarged. The spleen was not felt and the area not enlarged on percussion. The old appendectomy scar was noted. Extremities. There was an extensive scar of healed ulceration over the left tibia, partly covered by a thin shiny skin. In its lower portion there was an irregular granulating surface. The tibia beneath the scar area was enlarged. The deep reflexes were active. The plantar reflex was flexor. There was no tremor and no Kernig sign.

*Laboratory Findings*—Lumbar puncture on the day following admission yielded a spinal fluid containing considerable blood, so that cell count was impracticable. There were no organisms by smear or culture. Wassermann tests on blood and spinal fluid were negative. No acid fast bacilli were found.

in the sputum The blood culture was negative Roentgen-ray examination The lungs were negative except for some fibrosis in the second and fourth interspaces The heart measurements, center to right, 47 cm, center to left, 101 cm, transverse, 148 cm, longitudinal, 162 cm, aortic, 55 cm On the day following admission the red count was 2,800,000, hemoglobin, 48 per cent, color index, 0.8, white count, 45,200 An occasional sickle cell was present in the film made for routine blood study This, together with the other abnormalities present, suggested the diagnosis, and study of wet preparations confirmed it In fresh wet preparations sealed under a cover glass there were 6 to 8 sickle cells per high power field On standing, the sickle elements gradually increased in number and on the following day, about twenty hours after they were first set up, the preparations showed at least 95 to 98 per cent of sickle forms The deformed cells frequently showed coarse bristle-like projections of the cytoplasm, several in number and often of considerable length One hundred and twenty-two nucleated red cells were seen while counting 500 leukocytes They were usually normoblasts with occasional intermediates Vital staining showed 18 per cent reticulated cells There were occasional myelocytes The platelets numbered 400,000 per cu mm The blood serum was dark colored and gave a strongly positive nitric acid reaction for bile pigments The Fouchet test for bilirubin was positive Van den Bergh direct reaction was negative, indirect, strongly positive The Hay sulphur test for bile acids was negative The fragility test showed beginning hemolysis at 0.34 per cent sodium chlorid, and

*Blood Counts, Made at Intervals of a Few Days*

Date	Hemo- glo- bin	Red Blood Cells	Color Index	White Blood Cells	Lympho- cytes	Endo- thelial Leuko- cytes	Neutro- phils	Eosino- phils	Baso- phils	Neutro- phil Myelo- cytes	Nucle- ated Red Blood Cells	Reticu- lated Red Blood Cells
3/15	48	2,800,000	0.8	45,200	35.2	1.8	58.6	0.2	0.4	3.8	122	18%
3/18		2,780,000		28,400	34.0	3.0	61.2	0.6	0.8	0.4	190	
3/20	45	2,270,000	0.9	39,000	40.2	2.2	52.4	0.8	1.2	3.2	195	26%
3/22		2,000,000		53,800	33.0	3.6	57.2	1.0	1.0	4.2	762	
3/27	45	2,700,000	0.9	29,700	42.6	2.2	51.6	1.0	0.6	2.0	89	30%

complete hemolysis at 0.16 per cent Chemical examination nonprotein nitrogen, 36.7 mg, urea nitrogen, 15.4 mg, uric acid, 4.4 mg, creatinin, 1.5 mg, sodium chlorid, 310 mg Blood counts made at intervals of a few days are given in the table Five hundred leukocytes were counted in each case

Urinalysis specific gravity 1.014, acid reaction, trace of albumin present in repeated specimens, and always a few to moderate numbers of granular casts The color was seal brown, foam slightly yellow tinged Gmelin test for bile was negative although a slight but definite green was obtained with the Smith test There was a strong urobilin reaction By the method of Marcussen and Hansen the positive reaction persisted through dilutions of the urine, ranging from 1:00 to 1:400 Two hour specimens showed marked fixation of the specific gravity During a twenty-four hour period, all day specimens gave 1.014 with one exception, this giving 1.013, the twelve hour night specimen read 1.013 Day urine was 568 cc, night 630 cc, total for twenty-four hours, 1,198 cc Total chlorids calculated as sodium chlorid, for day urine, 8.52 gm, for night urine, 8.52 gm, a total of 17.04 gm A second specimen collected during the early pneumonia showed for the day urine 5.42 gm, for the night, 3.79 gm, a total of 9.21 gm

*Course of Illness*—For the first twenty-four hours the patient complained acutely of pain in back of head with posterior cervical and lumbar pain and soreness The temperature rose to 103.4 then dropped slowly and reached normal on the third day It continued, however, to show irregular fluctuations from 98 to 100 or 101 On the fifth day he complained of sore throat On the fourteenth day the temperature rose to 103, he developed a cough and complained



of pain in the chest. A few rales were present at the base of the left lung. Typical signs of bronchopneumonia appeared during the third week. Death occurred on the twenty-second day following admission.

*Necropsy*—The body was that of a well developed and well nourished negro man, 163 cm long. The pupils were equal, round and 4 mm in diameter. There was a yellowish coloration of the sclerotics with a distinct greenish tinge that was particularly noticeable in the upper hemisphere of the globe. There was slight pyorrhea, but the teeth were in fair condition. The base of the tongue was natural in consistency. There was a normal beard and well marked growth of hair in midline of trunk. The cervical and axillary lymph nodes were palpable, the inguinal nodes were slightly enlarged. The epitrochlears were not felt. In the right lower quadrant there was an old healed surgical wound. An extensive area of old scarred cutaneous ulceration was present over the left tibia. It was 15 cm long and 4 cm in greatest width. In its lower portion there was an area of active ulcer, measuring  $6\frac{1}{2}$  by 3 cm. The floor was covered by granulation tissue, the margins were thin and irregularly outlined. The underlying tibia bulged forward as two flattened mounds of bony hardness.

*Peritoneal Cavity*—Primary incision revealed a yellowish coloration of dermis, subcutaneous tissues and fasciae. The subcutaneous and peritoneal fat was orange colored. The muscles were deep red. The serosae were smooth and glistening. The appendix was absent. The mesenteric lymph nodes were not enlarged.

*Pleural Cavities*—The left contained about 150 cc of turbid yellowish fluid, the right about 300 cc of seropurulent fluid with much fibrin. The surfaces were covered by a loose film of bright yellow fibrinopurulent exudate. Only traces of the thymus gland could be made out.

*Pericardial Cavity*—This contained about 100 cc of clear greenish fluid.

*Heart*—Weight, 335 gm. Valve measurements were normal. The myocardium was flabby, dull red in color. The valves and endocardium were negative. The covering and lining membranes were yellowish in color. The coronaries were negative.

*Lungs*—On the left side the upper lobe was pinkish gray, and crepitant in the upper and anterior portion, reddish and more resistant with decreased crepitation in posterior third. The surfaces of the lower lobe were covered by a thin film of yellowish fibrinopurulent exudate. The dependent half was dense and dull red. Beneath the pleura were a few irregular, grayish areas and there was a single larger area of similar appearance forming the center of a bulging mound of increased density that was capped by a thickened layer of exudate. Section here revealed an irregular sharply outlined area of grayish softened material, extending inward as a column 15 cm long and from 4 to 5 mm in width. The smaller subpleural areas mentioned showed a similar gross picture. The sectioned lung was, in general, pink to red with many deeper red areas of slightly increased density. These often surrounded slightly dilated bronchial lumina that exuded abundant pus. There was one old peripheral scar with overlying dense fibrous adhesions. The bronchial mucosa was swollen, reddened and bathed in purulent exudate.

*Right Side*. All the lobes were of increased density. Their surfaces were covered by a layer of bright yellow fibrinopurulent exudate. On section, the surfaces were reddish and dotted with many deeper red areas. In some places the lung was collapsed, deep red in color and moist. In the lower lobe there was a peripheral wedge shaped area of firm yellow appearance with a softened granular center. It was like the areas already mentioned in the left lung. It was overlaid by a thick layer of dense fibrous exudate.

The bronchial lymph nodes were moderately anthracotic and moist.

*Spleen*—The weight of the spleen was 28 gm. It had the shape of a flattened wedge, the anterior surface forming its base while the hilum appeared at the middle of the posterior ridge. The base measured 7 by 4 cm and was pointed

at the poles. The greatest thickness from base to apex of the wedge was 2.5 cm. The organ was firm in consistency with a wrinkled capsule. The broad base showed numerous rounded slightly elevated nodulations with flattened summits. They were a slightly deeper red than the surrounding tissue and varied from 1 to 3 mm in diameter. Toward one pole, the ridge like surface of the spleen was interrupted by a rounded mass of soft deep red tissue. It measured 2 by 2 by 1.7 cm. The splenic artery showed no abnormality anywhere in its course and the veins likewise were free of gross lesions. On section, the splenic tissue was firm, dull red in color, with prominent, closely placed trabeculae and numerous vessels of relatively large size. The pulp tissue was evidently much reduced in amount. The splenic corpuscles were not made out. The most striking characteristic was the presence of many sharply outlined rounded areas of brighter red color that had the appearance of pushing the older parenchymal tissue aside. They were dotted everywhere throughout the organ, and at the periphery gave rise to the nodulations noted on external examination. The largest nodule formed the tumor-like mass already mentioned.



Fig 1—Spleen. The nodules of adenomatous hyperplasia stand out prominently as darker sharply outlined areas.

This, on section, was found to consist of a soft, almost gelatinous deep red homogeneous material sharply outlined against the surrounding parenchyma. The smaller nodules varied from 1 to 3 mm, in one case 4 mm, in diameter and showed on a smaller scale the gross characteristics of the largest mass.

*Liver*—Weight, 2,567 gm. Capsule smooth, color mahogany red. On section, the tissue was soft and friable. The cut surface was reddish with indistinct mottling of brown to yellow, sometimes suggesting the parenchymal network, but never showing a distinct pattern. The surface oozed a slightly turbid reddish material.

The gallbladder was filled with thick dark green bile and contained three small faceted calculi of greenish black color. The ducts were patent.

*Pancreas*—The gland was pinkish. The size and consistency were natural.

*Gastro-Intestinal Tract*—There was a slight "shaven beard" appearance in the lymphadenoid tissue of the ileum just above the valve. The solitary follicles of the colon were slightly enlarged in some regions.

*Suprarenals*—Weight 10 gm Externally, the glands were brownish On section, the cortex was brownish to brownish-yellow, the medulla china white and moderately abundant The pigmented zone was of normal width

*Kidneys*—Weight 310 gm The surfaces of both kidneys showed occasional irregular depressed scars Some were of considerable size They were located principally on the posterior surface and convexity The largest scar occurred on the posterior surface of the left kidney, where it formed a slightly irregular trough from 2 to 3 mm in width and reaching 3 mm in depth It extended from the hilum almost to the middle of the convex border, widening at the outer end On section the capsule was found to be slightly adherent, but the underlying surface was relatively smooth The cortex was from 6 to 7 mm in width There was slight generalized greenish-yellow coloration The glomeruli were prominent and the radial markings distinct Labyrinth columns were yellowish gray The most remarkable gross changes were found in the



Fig 2—Segment from right femur Specimen consists of anterior half of shaft as it was split off by usual method for inspection of marrow

pyramids A few of these were natural and a light dusky red in color For the most part they showed more or less extensive areas of greenish yellow, scar-like tissue that often formed a cap in the papillary region, but extended outward to occupy the whole middle portion of the structure, leaving only a narrow marginal column of natural appearance Again it formed narrow bands, extending from the papilla almost to the cortex There were also frequent hemorrhagic areas from 1 to 3 mm in size that often occurred about the margins of the scar-like lesions In many cases, these pyramidal lesions appeared to coincide with the surface depressions of the cortex There was slight yellowish mottling

*Bladder, Prostate and Testes*—These organs were free of gross lesions

*Aorta*—There was very slight yellowish mottling of the intima in the lumbar portion

*Head*—The calvarium showed no gross abnormalities The dura was slightly tinged with yellow Its sinuses were negative The arachnoid fluid

filling the sulci was of light yellow color. The fluid within the ventricles was also bright yellow. The cerebrum, basal ganglions, brain stem, pons, medulla and cerebellum were free of gross lesions except for a slight yellowish tinging of the tissues. The vessels of the base were negative. The middle ears were negative. The pituitary was of natural size.

*Spinal Cord*—Except for the yellowish coloration of spinal fluid and meninges, no gross changes were made out.

*Bones*—The right femur was exposed and about two thirds of its shaft opened for inspection. The marrow cavity was reduced in size. Its diameter

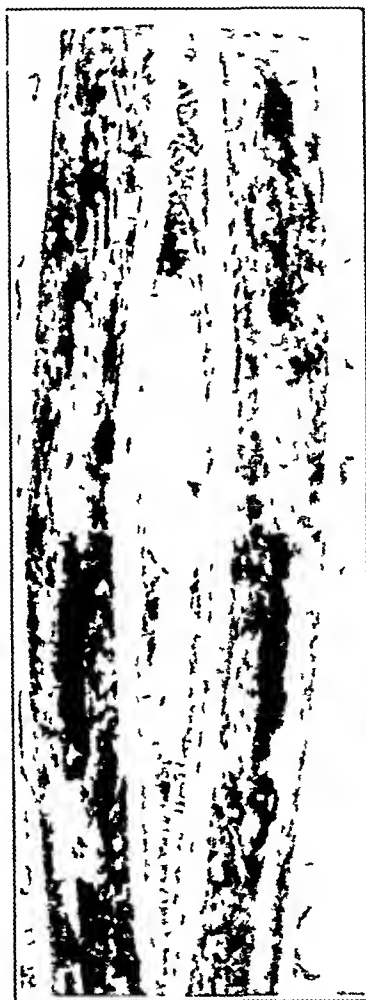


Fig 3—Left femur. The bone has been sawed longitudinally. Specimen shows greater portion of diaphysis.

was from 4 to 5 mm. The cortical bone averaged 1 cm in thickness. The outer 3 mm of the shaft was natural in appearance, but the inner portion had a concentric lamellated structure, with columns of dark red marrow tissue alternating with layers of equal width consisting of dense bone. Dark red marrow filled the upper cavity. At about the middle of the bone this was replaced by a greenish-yellow fat or fibrofatty material, and the cavity became tortuous and reduced to from 2 to 3 mm in diameter. Some islands of red marrow occurred in the lower half of the bone but they were of slight extent. The diaphysis of the left femur was removed and sawed longitudinally. The appearance was similar to that of the right femur (Fig 3). The diaphysis of the

left tibia was also removed and opened (Fig 4). The bone showed an elongated bulging enlargement toward the lower end. Cross section at the upper end showed a central fatty or fibrofatty marrow with much bony trabeculation. The inner half or two-thirds of the cortex was honeycombed and showed dense bony columns, interspersed with dark red areas of marrow tissue. The outer rim of cortex was of natural appearance. In longitudinal section the bone showed irregular distortion of its structures. The narrow peripheral zone of dense cortex outlined a wide inner zone of irregular medullization. At the upper and lower margins of the enlargement beneath the ulcer site there was



Fig 4—Left tibia. The irregular loss of substance on anterior edge is the result of exploratory chiselling before the bone was removed.

a deep extension of sclerotic bone that reached through the original marrow cavity to its posterior wall. At the middle of the enlargement the cavity was markedly widened and contained much cancellous tissue with deep red marrow. Above the enlargement there was deep sclerosis of the anterior wall of the shaft with practical obliteration of the marrow cavity, although a little marrow tissue survived in the cortex. Below the enlargement the cavity was irregularly obscured by transverse bone columns, but it reappeared at the lower end of the bone, where it was 1 cm in diameter and filled with hyperplastic marrow.

*Bacteriology*—Cultures from the heart blood showed the presence of *Staphylococcus hemolyticus*.

*Microscopic Examination*—Tissue was fixed in formaldehyd, Orth's fluid and Zenker's fluid. Paraffin sections were stained by the eosin methylene blue method, fat and iron reactions were applied to frozen sections of formaldehyd fixed material.

*Heart*—There were no abnormalities beyond slight fat formation in scattered groups of muscle fibers. There was moderate lipochrome accumulation.

*Lungs*—There was generalized congestion and edema. The bronchial lumina were filled with leukocytes and contained large numbers of chained cocci. These organisms occurred also within the lumina of several larger veins. There were scattered foci of intense leukocytosis and fibrinous exudate in the air spaces. The pleural surface was covered by a fibrinous network containing many leukocytes. In one section, an area of pneumonic exudation with necrotic center extended deeply from the pleural surface. Within the necrotic tissue there was intense growth of a chained coccus. The organisms spread laterally into the adjoining alveoli and were present in large numbers in the necrotic pleural covering.

*Liver*—The lobular structure was obscured by a fine, patchy fibrosis irregularly distributed through the central and midzonal regions of the lobules. Here in small areas the parenchymal cells were atrophied or destroyed. The sinusoids were more or less markedly dilated and engorged everywhere and the cell cords were relatively narrowed. In the sinusoids were large numbers of nucleated red corpuscles. They were often larger than the mature cells. Their nuclear material was abundant. It was often broken up into segments, the arrangement of which suggested mitotic figures but more commonly appeared as a basic-staining mass with ragged margins and coarse lobulations or as a network of coarse threads and bulbous enlargements. The sinusoids also contained occasional myelocytes sometimes grouped in small "islands." The endothelial cells lining the sinusoids often contained brownish pigment granules, and in the larger elements or Kupffer cells were occasional erythrocytes. Red cells and pigment granules occurred occasionally in endothelial leukocytes lying free in the vessel lumina. The liver cells showed a coarse mottling from prominence of the intracellular bile capillaries, which tended to retain the basic dye and which contained occasional small masses of inspissated bile. There was a moderate accumulation of brownish pigment granules in the liver cells. In some of the portal canals there was slight lymphocytic infiltration. Scarlet R showed only rare fat droplets. Under the Prussian blue reaction, the Kupffer cells were everywhere prominent as diffusely stained elements that showed also frequent iron-containing granules. Such granules occurred also with considerable frequency within the liver cells.

*Spleen*—Capsule and trabeculae were thickened. The trabeculae were crowded together and there was an obvious reduction in the amount of parenchymal tissue. The splenic corpuscles were usually of small size. Some of the central arterioles showed a fibrin deposit in intima and media or a wide wavy zone of hyalin beneath the endothelium. About many of the vessels was a concentric formation of fibrous tissue that was replacing the lymphoid structure. Fibrin deposits occurred also in this perivascular zone. There were occasional areas of scar formation that appeared to center about the foci of intense fibrin deposit. The fibrin was being replaced by collagen in some places while in others the threads became thickened and varicose and were encrusted with blood pigment and finally replaced by it. New and old collagen formations were closely approximated but occasional columns of the original parenchyma persisted here and there within the scar area. At the margins of the area the fibrin extended as dense networks into the adjoining parenchyma where foreign body giant cells often formed about it. The giant cells contained fine eosin staining threads or more often masses of blood pigment. Treatment with ferrocyanid demonstrated a rich iron content in these areas. The fibrin network in the walls of isolated vessels also gave an iron reaction.

The sinusoids of the pulp were engorged and the columns contained a thickened reticulum whose spaces showed few typical splenic cells but many erythrocytes. Erythroblasts and marrow cells appeared but they were few. There was no unusual pigment deposit outside the areas before mentioned nor was there any cellular phagocytosis. The tumor-like nodules noted in the gross description were rather sharply outlined. They consisted of a network of dilated sinusoidal vessels separated by pulp columns containing scattered splenic cells. Columns as well as vessels were engorged with blood. Within the vessels were many endothelial leukocytes containing red blood cells or more commonly crystalline masses of blood pigment. There was much of this pigment also in the lining endothelium of the sinusoids. Except in the marginal zone there were practically no larger vessels nor trabeculae and no definite splenic corpuscles.

*Gastro-Intestinal Tract*—Sections from the stomach showed slight focal infiltration of the mucosa by polymorphonuclear leukocytes. The peptic glands were normal. No lesions were present in the upper small intestine. In the ileum there was again a slight neutrophilic exudation in the mucosa. Some of the germinal centers of the Peyer's patch contained phagocytic endothelial leukocytes and occasional neutrophils, while a few eosinophils and neutrophils were scattered through the lymphadenoid tissue.

*Pancreas*—In an occasional group of end pieces there was moderate neutrophilic infiltration. A few of the gland cells were degenerating and their cytoplasm was at times invaded by neutrophils. The parenchymal cells including those of the islets contained a considerable amount of fat in the form of fine droplets.

*Suprarenals*—These glands were negative except for well marked postmortem degenerative changes in the cortex.

*Lymph Nodes*—Sections were cut from bronchial, inguinal, mesenteric and para-aortic groups. The histology was the same in all, except that in the bronchial nodes there was a direct extension of the pulmonary inflammation as evidenced by the presence of polymorphonuclears in sinuses and parenchyma together with two small abscess cavities in the cortex. Scattered through all groups were a few marrow cells. Most of these were of the early type with deeply basophilic cytoplasm. There were, however, many eosinophilic and an occasional definite neutrophilic granular form. Rarely, a myeloblast was caught in mitosis.

*Kidney*—In general, the glomerular tufts were enlarged and the spaces narrowed. Lobulation was indistinct. The capillaries were engorged and contained numerous polymorphonuclear with occasional endothelial leukocytes. There was little fibrin formation. The cells of the convoluted tubules contained a yellow pigment and the lumina were filled with a serous coagulum. Pigment deposit was marked also in the distal segments. There were occasional narrow radial scars. Sections through the areas of gross scarring showed identical lesions on a larger scale. In these areas there was marked proliferation of the glomerular epithelium with later fibrosis. The epithelium formed a wide crescent that compressed the dome of the tuft, and as fibrosis took place tuft and thickened capsule were converted into a common mass. Axial remnants of the capillary loops persisted in some cases, and here the surviving vessels themselves appeared free of lesions. In many glomeruli the dome of the capsule was little or not at all thickened but there was a dense fibrotic disk radiating in the capsule from the base of the tuft or ascending into one of its loops. Here also the eventual occurrence was a gradual centripetal fibrosis of the vascular structures. In the areas of gross scarring all the glomeruli were affected and many were completely sclerosed. There was advanced atrophy of the tubules and the stroma was infiltrated by large numbers of lymphocytes and plasma cells with occasional neutrophils and eosinophils. Many of the surviving

tubules, particularly in the middle and lower zones of the cortex contained casts. The largest sectioned area of injury spread widely in the subcapsular zone. Below this it narrowed rapidly toward the medulla but continued to show inflammatory exudate, together with fibrosis and tube changes. Beginning at the level of the junction of the upper and middle third of the pyramid, there was a sharply outlined area of interstitial fibrosis into which some of the tubules could be followed for a short distance. For the most part, however, this area contained only widely spaced shadows of atrophied tubules and rare blood vessels. There were occasional excretory tubules, the epithelium of which contained many coarse brownish yellow pigment granules. Occasional neutrophils occurred, especially about the degenerating tubules. No arteriosclerotic changes could be made out in large or small arteries. The petechial areas noted in gross description as occurring in the pyramids appeared microscopically as collections of widely dilated capillary vessels deeply engorged with blood that carried many leukocytes. The tightly compressed red cells in some of the vessels showed considerable elongating deformity. Scarlet R demonstrated a patchy fatty change in the distal portions of the cortical tubules, particularly in those of scattered medullary rays. The fat became more prominent in the collecting tubules of the medulla and was especially marked in those lying within the scar areas. Much iron-containing pigment was demonstrable, particularly in the convoluted tubules.

*Thymus Gland*—The parenchyma was represented merely by small columns or islands of typical highly vascular tissue embedded in fat. There were no typical Hassall's corpuscles. There were, however, occasional small sharply outlined rounded collections of cells with large vesicular nuclei and relatively large cell bodies of clear or faintly reticulated eosin staining cytoplasm. Such cells were crowded together as a mosaic, showing distinct contact lines between adjoining cells. Again, there were similar cells that occurred in irregular sheets of indistinct outline.

*Testes*—Spermatogenesis was active. There were no lesions.

*Aorta*—Negative.

*The Cerebral Cortex, Basal Ganglions, Cerebellum, Medulla and Cord*—Negative.

*Choroid Plexus*—Negative.

*Pituitary Gland*—Acidophilic and basophilic cells of the anterior lobe were present in normal ratio. A few lymphocytes and plasma cells occurred in the pars intermedia and posterior lobe.

*Bone Marrow*—The tissue was a closely crowded mass of erythropoietic and leukopoietic cells. There were many myeloblasts, sometimes in mitosis, and larger numbers of neutrophilic myelocytes. There was about the usual proportion of eosinophilic myelocytes. There were occasional eosinophilic and fewer neutrophilic polymorphonuclear leukocytes. Particularly striking was the great number of nucleated red cells. These often showed a well marked arrangement in columns or islands, separated by areas in which the cells were predominantly myeloblastic. The nuclei were often broken up by karyorrhexis. Megakaryocytes are rather more frequent than normally. In a few cases one or two neutrophils were included within the cytoplasmic body of these cells. The cells of the reticuloendothelium occasionally contained golden yellow crystals of blood pigment.

*Bone*—Transverse sections were cut through the upper ends of the femur and the left tibia. They showed a slightly irregular periosteal surface with frequent Haversian depressions and traces of recent osteogenesis. The outer zone of the cortex was natural but toward the middle of the bone it quickly became invaded irregularly by larger and smaller spaces containing hyperplastic marrow tissue. Some of these spaces appeared to cut through the older lamellae. Smaller examples are recognizable as enlarged Haversian or Volkmann canals.



They may approach to within 1 mm of the periosteal surface. The medullized bone extended in some sectors to the center of the shaft, and consisted of a close network of wide dense trabeculae outlining spaces filled with hyperplastic marrow. Again, there was a central or paracentral area, with delicate cancellous bony framework and wide spaces filled with a loose fibrous granulation tissue. In some sections a wide area of acellular hyaline material occurred at the center of this scar tissue. Scattered through it and extending somewhat into the peripheral loose fibrous tissue were many larger and smaller collections of delicate golden yellow threads of crystalline brilliance. In some cases they were surrounded by a thin zone of lymphocytes while occasional endothelial leukocytes in the vicinity had phagocyted the pigmented threads. The trabeculae nearest the necrotic center of such an area showed marginal necrosis, but in the granulation tissue zone were foci where old trabeculae were being added to or new ones appeared to be in the course of construction through a process of intramembranous osteogenesis. Peripherally, the granulation tissue with its occasional foci of lymphocytic infiltration merged at times into fatty marrow and this in turn was replaced by a highly cellular red marrow. Some of the more central marrow columns showed areas of hemorrhage with some necrobiosis and considerable fibrin formation.

The bone from which these sections were cut was hardened in Kaiserling's fluid. Unlike the cells in blocks fixed in Zenker's fluid, the erythrocytes here showed marked deformity. They exhibited all the distortions of shape previously seen in fresh blood preparations. They were particularly liable to great elongation. As seen within an engorged vessel, they often assumed a concentric whorl appearance.

#### SUMMARY OF GROSS AND MICROSCOPIC DIAGNOSES

In this case, examination revealed Acute streptococcic bronchopneumonia with early empyema, streptococcic bacteremia, anemia associated with sickling deformity of the red blood cells, icterus, splenic atrophy, splenadenoma, chronic osteomyelitis with repair and hyperplasia of marrow and osseous tissue, chronic periostitis and osteitis of tibia, acute intracapillary and chronic productive capsular glomerulonephritis, chronic hepatitis, metastatic hematopoiesis in liver, spleen and lymph nodes, hemosiderin pigmentation of liver and kidneys, chronic pretibial skin ulcer, cholelithiasis.

#### COMMENT

*Etiology*—As with many other conditions whose causation is obscure, it was at first suspected that this disease might be a manifestation of tuberculosis or of syphilis. There has been no evidence to support either assumption. Herrick's patient was a West Indian, and had been in this country but three months when examined. He had suffered an attack of yaws ten years previously, but had recovered after a year. All the other patients have been natives of U. S. Four cases have originated in Virginia, one in Missouri, two in Maryland. Sydenstricker's two detailed cases occurred in children, presumably natives of Georgia. The subject of this report was born in southern Alabama and had lived all his life in this state. The disease appears then to be widely distributed. In all cases, repeated search has failed to reveal the presence of parasites in blood or stools. One of Sydenstricker's patients had a history of malaria six months previously, but had recovered

Blood cultures have been negative in all cases investigated Emmel<sup>8</sup> suggested the possible inheritability of the disease Huck and Sydenstricker have offered valuable evidence to support this idea From a study of affected family groups, Huck concluded that the disease is transmitted according to the Mendelian law for the inheritance of a single factor and finds that the sickle cell condition is dominant over the normal

*Symptomatology*—The most prominent symptom is a chronic anemia that makes its appearance in childhood Associated with it are the complaints common to any anemia The patient is weak easily fatigued, breathless on slight exertion Sometimes there is edema of the feet and ankles, dizziness and headache Night sweats are common More significant is the history of recurrent attacks of acute illness characterized by moderate or severe pain and stiffness in muscles and joints without evidence of local inflammation There is often sharp epigastric pain which is especially marked after eating This may be the only complaint Sydenstricker emphasizes left hypochondriac pain Fever accompanies the attacks It is usually of low grade but may reach 101 F In this case it touched 103 F The duration of the period of relapse is ordinarily from one to two weeks, of the remissions, several months or even years Chronic leg ulcer has been present in the adult cases In the patient of Cook and Meyer it made its appearance at the age of 5 years, in Herrick's patient at about 10 years, and in our own at about 15 years It appeared at 20 and 21 years in the cases of Washburn and Mason and was absent in both of Sydenstricker's patients (aged 5½ and 6 years, respectively) Huck states that these patients are unusually susceptible to infections, particularly tonsillitis and pneumonia, and that they seldom live beyond the age of 30 years

These are the chief points in active cases of the disease Systematic examination of patients' relatives and of nonselected individuals has, as already noted, brought to light evidence that the disease exists in many degrees of severity Huck divides his cases into three groups as the patient showed symptoms that were (1) absent, (2) mild and (3) severe Those with absent symptoms "go through life as normal persons" Those with mild symptoms complain only of occasional periods of weakness and fatigue and possibly of slight pain in muscles and joints The one feature common to all types is the sickling of the red cells *in vitro* Sydenstricker accepts sickling of the red cells as pathognomonic but believes that subjective symptoms are always present

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<sup>8</sup> Emmel, Victor E A Study of the Erythrocytes in a Case of Severe Anemia with Elongated and Sickle-Shaped Red Blood Corpuscles, Arch Int Med 20 586 (Oct) 1917

in mild form at least and that these are accompanied by definite objective signs. He divides the disease merely into "active" and "latent" phases.

*Objective Signs*—One of the most striking objective signs is a peculiar greenish or greenish-yellow scleral discoloration. According to Sydenstricker, this is constant in both active and latent cases. In the original case, Herrick noted "a tinge of yellow", all other authors have reported a greenish or greenish-yellow color. In our case physical examination made before the diagnosis was established records greenish sclerotics. This chart notes also a suggestion of icterus in the skin. The only other mention of this condition is made in one of Sydenstricker's cases, yet if the necropsy findings in our case may be taken as typical there is no doubt that there is a very definite jaundice. The mucous membranes are pale. General glandular enlargement has usually been noted. In our case only the inguinals and some posterior cervicals were suggestive of enlargement. The heart is usually slightly enlarged and there may be a soft systolic murmur and an accentuated pulmonic second sound. The lungs are negative. The blood pressure is low, from 100 to 105 systolic and from 55 to 70 diastolic. The pulse is rapid and may show marked hourly variations in rate. The liver is usually palpable with its margin from two to three fingerbreadths below the costal margin. It may be slightly tender. No spleen is palpable. The reflexes are active. Leg ulcer or scar is usually found at least after childhood and may occur even in latent cases.

*Laboratory Findings*—The blood and urinary findings as given for our present case are in practically all respects typical. In active cases the red count is low (from  $1\frac{1}{2}$  to 2 millions), and the hemoglobin is proportionately reduced so that the color index varies from 1 to a little above 1. Bleeding and clotting time are normal. The platelets are normal or slightly increased in number (from 300,000 to 500,000). One of our counts showed 400,000, a second 500,000. There is some anisocytosis and poikilocytosis and often well marked polychromatophilia. Nucleated red cells (normoblasts, intermediates or rarely megaloblasts) are usually present. In our case they appeared in much larger numbers than in previous cases. On one occasion there was a veritable shower of these forms so that they outnumbered the leukocytes by 50 per cent. Reticulated red cells are numerous (from 10 to 35 per cent). There is well marked bilirubinemia.

The white count varies widely. In active cases it usually ranges from 10,000 to 20,000, but has reached 64,000. The eosinophils and basophils may be slightly increased and a few myelocytes are present. One finding that has attracted considerable attention since first noted by Emmel is the presence of endothelial leukocytes (the so-called large mononuclear and transitional cells) that have picked up erythrocytes

and carry them within their cytoplasm. It has been suggested that this phagocytosis of the red cells may be a factor in the causation of the anemia. There is variance in the opinions as to its frequency. Sydenstricker states that it is always found, but Huck disagrees with this position. In our case, not a single example was found in the numerous slides studied, nor is there much evidence of its occurrence even in the visceral blood spaces.

Sickling of the red cells is of course the outstanding phenomenon. In our own case, smears made as for routine blood study always showed a few characteristic forms and this appears to be true generally for active cases. Complete demonstration of the sickling can be had, however, only by sealing a fresh drop of blood under a glass cover and studying after an interval of several hours or longer. The percentage of the cells that take on the bizarre shapes is said to vary proportionately with the severity of the disease. Emmel<sup>8</sup> who first studied "culture" preparations in the blood of Cook and Meyer's patient and in that of her father, found that "sickles" disappeared from the patient's fresh blood during remission and that they were completely lacking in the father's fresh blood. The latter had never shown active symptoms. In both, sickling gradually developed in sealed preparations, but the father's never showed as high a percentage of deformed cells as did the daughter's. These findings have been substantiated by later work.

It is stated that the red cells show normal or decreased resistance to hypotonic salt solutions.<sup>6</sup> Sydenstricker states<sup>7</sup> that there is a "slight extension of the range of dilutions in which hemolysis occurs." In our case there is considerable downward extension of the range through which the red cells resisted complete hemolysis.

The urine is of a deep brown color, due to the presence of urobilin. Our patient stated that during remission this color disappeared. There is a trace of albumin and a few casts are always present. The specific gravity is fixed, usually at a level of about from 1.010 to 1.012, in our case at a slightly higher level. There is good phenolsulphonephthalein output. It is stated that gastric analysis shows diminution or absence of free hydrochloric acid. Blood cultures have always been negative and no parasites have been found in the blood or feces. The Wassermann blood test is negative and there is no evidence of any relationship with tuberculosis.

*Observations on the Sickling Phenomenon*—Emmel found the red cells unusually soft and pliable. He tried to discover by simple experiment whether the foundation for the sickling change lay in the cell itself or in the plasma. While the evidence showed that the principal factor lay in the cell, he concluded that both cell and plasma may be abnormal and that the altered plasma may in some way modify the osmotic rela-

tionships of the cell's lipoidal surface membrane. As a result the concavity that transforms the originally globular erythrocyte into a biconcave disk is displaced toward the cell margin, where it forms a lateral film that disappears and leaves only a thickened marginal crescent of the cell. Huck and Sydenstricker have extended Emmel's experiments. Both conclude that the real abnormality lies within the red cell. Cells from a case of the disease show the sickling change in normal serum but the serum is without effect on normal red cells.

Emmel found that sickling was "not as marked" in a free hanging drop of blood as in the preparation spread beneath a cover glass. This was noticed in our early specimens and repeated trial confirmed the observation. We failed also to get sickling in cells received directly into normal saline or in citrate in saline. This is contrary to Huck's findings. Sydenstricker<sup>5</sup> states that cells suspended in 0.85 per cent sodium chlorid and in isotonic glucose solutions underwent no changes even after the lapse of a week. His conclusion is that serum is essential to the change. He finds also that bile and bile pigments or sodium glycocholate in high dilutions accelerate the red cell changes and that cold inhibits them. No disturbances are produced in rabbits by the inoculation of diseased blood.

Cell deformity did not occur in every preparation made in our case nor was it uniform throughout the area of any single preparation. On one occasion, three cover glass preparations were made. All failed to develop any sickling. On another day, one of three preparations failed to show it although all three had been prepared, so far as we could determine, in the same way. In a given preparation, sickling occurred at different rates of speed and in different percentages in different zones of the drop. The thicker layer usually formed at the margins of the cover glass often dried without showing cell deformity, in the middle zone where the layer was somewhat thinner there was marked rouleaux formation and sickle cells appeared slowly and in relatively few numbers. The optimum location for the occurrence of deformity was in the thinner portion of the film located usually toward the center or sometimes toward one side of the cover, where the film was compressed by maximum approximation of cover to slide. Taken in conjunction with the fact that very few deformed cells can be found in a hanging drop preparation this suggests that deformation is a physical change dependent on a peculiar lability of the red cell. The absence of deformity in cells received into isotonic salt solutions and mounted in them in the usual way suggests, however, that there is also a physicochemical factor involved. Little or no deformity occurs within the blood vessels. Blood taken from the heart and from the longitudinal sinus twenty hours after death showed sickle cells in about the same percentage as blood taken during life. One-half hour

later there were about 50 per cent deformed cells and in six hours, close to 100 per cent. In tissues fixed in Zenker's fluid and embedded in paraffin the erythrocytes show no abnormality. It is of interest, however, that after fixation in 10 per cent formaldehyd and paraffin embedding, blocks from the same tissues show marked sickle deformity. The same is true of tissue hardened in Orth's fluid and rushed rapidly through the paraffin series. The proved superiority of Zenker's fluid as a cell preservative admits no doubt that the deformities seen in fixed tissues are artefacts due to physicochemical changes taking place in the erythrocytes during fixation.

*Pathology*—The following discussion is based largely on study of the tissue changes in a single case. Such conclusions as may have been arrived at must be held subject to revision. In the case studied, the presence of a streptococcus pneumonia with bacteremia may have obscured or changed preexisting lesions and added new elements well calculated to confuse the picture. There are, however, distinctive lesions that must have antedated the fatal infection and these appear to fit together into a fairly definite pathologic syndrome consistent within itself, and generally in accord with the clinical findings not only in this case but in others.

As would be expected, the outstanding lesions are those of the hematopoietic system. All three of the long bones examined show rather remarkable gross and microscopic changes. The picture is essentially that of a chronic infectious or toxic injury of the marrow tissue and medullary bone with subsequent repair processes and compensatory hyperplasia. There is focal necrosis destroying the soft tissue and injuring the bone trabeculae. The necrotic marrow is being replaced by a loose granulation tissue while bone repair is also in evidence. At times the process of new bone formation has proceeded so far as to narrow and distort or even to destroy the original marrow cavity. Driven from its original site, the marrow tissue appears in some places to have shifted outward into the thickened cortex, where a process of medullization had opened for it a series of wide crevices in which there has appeared a regeneration and even a compensatory hyperplasia of the blood forming cells. In the tibia of the ulcer bearing leg, the picture is complicated by a periostitis and osteitis beneath the ulcer site. Here foci of intense osteosclerosis extend deep into the bone substance, but in the middle of the bony enlargement there is also a rarefying process that has hollowed out a wide bone cavity. This is filled with hyperplastic marrow, so that despite the practical obliteration of the marrow space at some levels of the bone its total capacity is probably greater than the normal. In the hyperplastic foci the marrow tissue is actively at work. The formative cells of the leukocytic series

are prominent but the greatest degree of activity is shown by the erythrogenic elements. These are often arranged in distinct islands like those of an embryonic marrow. The megakaryocytes likewise are more numerous than in the normal adult bone. During life, all these circumstances were reflected in the circulating blood with its many nucleated red cells, high white count and increased platelet content. In all three of the previous necropsies, the marrow has been reported as hyperplastic but there is no mention of lesions affecting the bone substance.

The spleen is unusually small. The same was true in Huck's case and in the first of Sydenstricker's. In the latter's second case it was enlarged and contained multiple infarcts. The noteworthy shrinkage is explained by the atrophy of the pulp tissue. The lymphadenoid tissue of the corpuscles has suffered to less extent but here also there is slow fibrous replacement proceeding outward from the central arterioles. Here and there through the tissue are peculiar scar areas of microscopic size somewhat suggesting healing infarcts, but probably best interpreted as focal areas of toxic parenchymal destruction. They may be likened to those found in the bone marrow. In both situations the affected areas show much fibrin formation but little else in the way of inflammatory change. In neither case is the exact manner of origin plain, although it can be better understood in the bone marrow than here. The fibrin laid down in the walls of isolated blood vessels offers evidence that some toxic substance is at work. It is probable that the pulp lesions are built up about foci where fibrin deposits have occurred in or about the smaller pulp vessels. The fibrin is of varying age as evidenced by the fact that at the margins of scar areas, where possibly the cause is still operative, the fibrin is natural in appearance and staining reaction while in other places it appears to have absorbed more or less blood pigment. In older portions of the lesions it is being replaced by dense fibrous tissue. Not the least puzzling feature is the presence of the many rounded tumor-like areas of homogeneous dark red rather soft tissue. In the gross, they are sharply circumscribed and unlike the irregular blotches of true hemorrhage. Further, they distend the capsule as scattered flattened nodules and the largest representative is elevated above the surface in the hilum region as a distinct mass, the naked eye appearance of which strongly suggests that of a small accessory spleen. Microscopically they consist of a poorly developed splenic pulp engorged with blood. The engorgement, together with the abundant evidence of erythrocytic destruction, might be urged in favor of the view that they are only areas of hemorrhage. But the general formation as well as the absence of larger vessels and of well developed splenic corpuscles is believed to indicate rather that they are regenerative

foci of hyperplastic splenic tissue, the so-called "splenadenoma" Such younger areas might conceivably be active, while the older parenchyma has become atrophied and relatively functionless

The changes in the liver are those of an active attempt to dispose of unusual amounts of free blood pigment In addition, there is evidence that a certain amount of hematopoiesis is taking place The sinusoids contain great numbers of red cells, many of them of large size Some appear to contain mitotic figures The occasional small collections of marrow cells convey a definite suggestion of metastatic marrow tissue A moderate amount of bile pigment is present in the parenchyma, but it is by no means as abundant as would occur with blockage of the bile channels In passing, it may be recalled that the patient's serum during life was found to give a negative direct but a positive indirect Van den Bergh test for bilirubin The anatomic findings support the claim that such a reaction indicates a toxic rather than an obstructive jaundice

There is an acute intracapillary glomerulonephritis and, particularly in the areas of gross scarring, a well defined chronic productive capsular glomerulonephritis In its irregular focal distribution, the latter lesion does not conform to the usual picture in healed glomerulonephritis Focal scarring is known to occur, however, and it is probably unnecessary to set such cases apart in a separate group as is done by Lohlein In Sydenstricker's first case, the child, aged 5½ years, showed well defined renal disease with large, pale finely scarred kidneys presenting the microscopic picture of acute intracapillary glomerulonephritis and pericapsular fibrosis The condition of the kidneys is not reported for his second necropsy In Huck's case, the kidneys are described as small and scarred with adherent capsule No microscopic examination is reported, but in a subject aged 17 years, such a gross picture would suggest the possible presence of a chronic glomerulonephritis There seems, then, to be a pronounced tendency toward the appearance of acute and chronic glomerulonephritis in these cases The question arises whether this may be primary or secondary to the hemolytic phenomena, or whether both result from the activity of a single factor The latter view seems most plausible Both may result from toxic substances producing these and other lesions discovered Such a toxin might originate in a streptococcus infection Certainly the streptococcus is the organism most commonly proved as the source of injury to the glomerular apparatus In our case we know that a virulent streptococcus infection is associated with at least the present glomerular disease The medullary scarring is probably to be referred to the action of the same agent that produced the glomerular disturbance In many cases it is established in continuity with the cortical damage, although this



is not proved for every area. The marginal dilatation and overfilling of the capillary vessels is perhaps an expression of the hemorrhagic character often exhibited by glomerulonephritis.

#### COMMENT

From a survey of the clinical and pathologic findings described, certain tentative conclusions may be justified. That the disease is a true hemolytic anemia is clear. The clinical picture is dominated by evidence of marked blood destruction. There is generalized icterus with marked urobilinuria and bilirubinemia. The red count is low and unusual numbers of nucleated and reticulated cells are present in the circulation. Much hemosiderin is deposited in liver and kidneys. The disease is not pernicious anemia nor is it hemolytic jaundice, although in certain features it resembles both. It is like pernicious anemia in its long course with intermittent remission and relapse. Clotting factors are normal and the erythrocytic resistance to hypotonic salt solutions is normal or even increased. It is unlike it but on the contrary similar to hemolytic jaundice in its marked familial character and jaundice. The platelet count is high and unusually high percentages of reticulated erythrocytes occur in the blood. In the fresh state the red cells show no noteworthy morphologic nor tinctorial changes except for the pathognomonic sickling. The markedly atrophic spleen sets the disease off as apparently distinct from pernicious anemia and even more sharply from hemolytic jaundice, splenic anemia or other splenomegalic blood destructive condition. It is to be noted, however, that if the foregoing interpretation of the splenic nodules is correct, there may be an element of "hyper-splenism" in the pathogenesis of the disease.

Two interesting characteristics are generally accepted as constant for the disease. These are its familial nature and its restriction to persons of negro blood. Many of the blood dyscrasias show more or less distinct inheritability and the familial character offers no new problem. But the racial specificity is unique. If found to hold true, this would indicate that the primary basis for the disease must be laid in conditions far removed from any possible accident of environment and even from any immediate familial influences. To cover such a conception we must assume that the disease depends primarily on some fundamental racial peculiarity of the blood-forming tissues. An interesting question is raised by the fact that many persons have been discovered whose blood cells show the sickling phenomenon, but who appear otherwise to show no departures from the normal. Should such persons be considered as suffering from sickle cell anemia? The condition here might perhaps better be conceived of merely as a constitutional anomaly, a "status

hemicus" comparable to the well known "status lymphaticus." As in the latter condition, the state may not be incompatible with good health until such time as the organism may be subjected to special stress of a type capable of bringing to light the inherent weakness. The nature of such excitant is, of course, problematical. It might be some toxic agent, acting directly on the hematopoietic tissues. Rather more probable would be some nutritional or metabolic disturbance, particularly in view of the negro's frequent dependence on a poorly selected and insufficient dietary. The bones and marrow are sensitive to metabolic upsets. In a case of fatal rickets in an infant studied recently, the long bones showed extreme fibrosis of the marrow while the shaft had become a loose cancellous structure containing islands of a marrow that seemed to be struggling to re-establish itself in its former place of residence. The lesions in the present case suggest to a certain degree the adult prototype of such changes. In the infant, there was a pronounced migration of marrow cells of all types into liver, spleen and lymph nodes. In the present case there is a suggestion of similar metastasis. The infant's blood carried many more immature cells than were present here.

There is the further possibility that infection may be the immediate exciting agent in the production of the acute seizures typical of the fully developed disease. There is a certain amount of direct evidence in favor of this view. Subjects of the disease are said to be peculiarly liable to infections and particularly to tonsillitis. The intermittent character of the attacks may be due to a recurrent lighting-up of some persistent focus of infection. Here, indeed, might be a reason for a tendency toward relapse after exposure to cold. The phagocytosis of red cells by endothelial leukocytes in the blood stream, as noted in other cases, is a phenomenon that is well known to occur in acute or chronic sepsis and particularly in infections by the streptococcus. In our present case there was at least terminal streptococcus infection with characteristic glomerulonephritis, and it is perhaps significant that the older renal lesions found at necropsy are likewise of a type often associated with streptococcus infections. It is further noteworthy that in previous cases studied by necropsy there is evidence of similar renal disease. The fever accompanying relapse may indicate infection although it may, of course, result from the active hemolysis itself or from some nonbacterial disturbance of bodily metabolism underlying the hemolysis.

#### SUMMARY AND CONCLUSIONS

Sickle cell anemia has been held to constitute a definite disease entity. The present clinical and pathologic study of a well defined case is believed to confirm that view. Characteristic signs and symptoms are readily demonstrable by clinical and laboratory methods, while post-mortem examination reveals interesting lesions particularly affecting the hematopoietic system.

The number of cases thus far studied at necropsy is too limited to allow the formulation of any far-reaching conclusions as to the exact nature of the disease. A tentative working hypothesis may, however, be proposed. The condition may consist in an underlying status, determined primarily by deeply rooted racial characteristics and brought into clinical evidence in occasional persons through the immediate action of toxic, metabolic or infectious exciting agents. There is a certain amount of evidence favoring the view that this immediate causative factor is bacterial and particular suspicion is directed toward the streptococcus.

# THE PRODUCTION OF EXPERIMENTAL DIABETES INSIPIDUS \*

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## INTRODUCTION

The nature of that anomaly of metabolism known clinically as diabetes insipidus is not clear. One reason is its infrequency. Only fifteen cases were found in a recent study<sup>1</sup> of the records of over 175,000 admissions to the Presbyterian Hospital. Statistics, largely from American hospitals, compiled by Williams<sup>2</sup> give an incidence of about nineteen cases in each 100,000 admissions. It has been found difficult to hold patients suitable for metabolic study under extensive experimental observation<sup>3</sup>. The condition is chronic, cases are usually ambulatory and there is not the fear of complications, such as the coma of diabetes mellitus. Thirst experiments especially are not well borne, owing to the severity of this symptom. An attempt to reproduce the disease experimentally in dogs has consequently seemed desirable.

Polyuria, usually transient in character, has frequently been produced by experimental injury to different parts of the brain. Bernard<sup>4</sup> noted polyuria subsequent to puncture of the floor of the fourth ventricle just ahead of his diabetic pigûre. Eckhard<sup>5</sup> added other regions, the pons, a lobe of the cerebellum, injury to which resulted in an increased urinary output. Kahler<sup>6</sup> was even able to produce in rabbits polyuria of weeks' duration, by injection of silver nitrate into the floor of the fourth ventricle. Camus and Roussy<sup>7</sup> found that puncture of the area about the stalk of the hypophysis, the optopeduncular area, commonly resulted in polydipsia and polyuria, even of months' duration.

Experimental procedures on and about the hypophysis are frequently followed by polydipsia and polyuria. This was noted as early

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<sup>1</sup> From the Department of Surgery of Rush Medical College, and the Hull Anatomical Laboratories of the University of Chicago

1 Unpublished data

2 Williams, J R. *Endocrinology and Metabolism* 4 861, 1922

3 Christie, C D, and Stewart, G N. Study of a Case of Diabetes Insipidus with Special Reference to the Mechanism of the Diuresis and of the Action of Pituitary Extract in It, *Arch Int Med* 20 10 (July) 1917

4 Bernard, Claude. *Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme*, Paris, 1859, Vol 2

5 Eckhard, C. *Ztschr f Biol* 44 407, 1903

6 Kahler, O. *Ztschr f Heil* 7 105 1886

7 Camus, J, and Roussy, G. *Presse med* 22 517, 1914

as 1892 by Vassale and Sacchi,<sup>8</sup> who attempted to destroy the hypophysis in dogs and cats through the buccal route. It has been extensively confirmed by many investigators, notably Cushing<sup>9</sup> and his associates. It is not so clear, however, that the increased water transport is subsequent to pituitary disturbance. Accumulating experimental evidence, in the work of Camus and Roussy,<sup>10</sup> Houssay,<sup>11</sup> Hanchett,<sup>12</sup> and Bailey and Bremer,<sup>13</sup> points rather to injury of the hypothalamus in the region of the pituitary stalk.

Hanchett,<sup>14</sup> in his experiments, found in Dog 2 that polyuria followed an accidental burn of the mammillary bodies, and that necropsy revealed the "hypophysis intact." In extensive later experiments in this laboratory, he was able to produce transient polyurias consistently by traction on the pituitary stalk and attached floor of the third ventricle. He concluded that "The degree of polyuria was roughly in proportion to the amount of traction."

Consequently, in attempting to produce polyuria and polydipsia of long duration, an experimental diabetes insipidus, it seemed logical to injure the brain in the area about the attachment of the hypophysis. The general plan followed was to expose this area, injure it, and keep the animals under subsequent daily observation in metabolism cages. At the end of an experiment the dog was killed, necropsied, sections made of the viscera and serial sections prepared of the hypophysis and adjacent hypothalamus.

Among six experiments on animals with polyuria it was possible to produce one lasting for nearly five months. An extensive study of this case has shown it to correspond most closely to those clinical cases of diabetes insipidus, known as primary or functional polydipsias.

Both young and adult dogs were used throughout the experiments. The best results were obtained with young animals. The cages were kept clean and the food and water supply controlled, as well as the urinary output. In the later experiments variations in the water exchange, resulting from operation and other procedures, were carefully noted. Urinary solids, specific gravity, chlorid concentration reaction, and presence of sugar, acetone or albumin were determined daily in

8 Vassale, G., and Sacchi, E. *Riv sper di freniat* **18** 525, 1892, *ibid* **20** 525, 1894.

9 Crowe, S. I., Cushing, H., and Homans, J. *Bull Johns Hopkins Hosp* **21** 127, 1910.

10 Camus, J., and Roussy, G. *J de physiol et de path gen* **20** 509, 1922.

11 Houssay, B. *Endocrinology* **2** 94 (April-June) 1918, *Compt rend Soc de biol* **81** 381, 1918.

12 Hanchett, M. *Am J Med Sc* **163** 685 (May) 1922.

13 Bailey, Percival, and Bremer, Frederic. *Experimental Diabetes insipidus*, *Arch Int Med* **28** 773 (Dec) 1921.

14 Hanchett, M. *Proc Inst Med Chicago* **3** (Feb) 1921.

animals with polyuria over periods of from one week to four months. Some idea of the normal water exchange and associated phenomena has been gained by a similar study of twelve normal control animals over periods of from one week to three months. More limited studies were made of the blood chlorid in normal and polyuric animals.

In an attempt to determine something of the nature of the increased water exchange, various tests were made on the animals with polydipsia and polyuria, such as phenolphthalein elimination, water restriction, starvation, giving chlorids, varying the diet and injecting pituitary extract.

#### METHODS

In order to expose the hypothalamic region, two routes of approach were followed, the buccal and the temporal. The buccal route was used by Dasie, described by Marinesco<sup>15</sup> and later fully outlined and illustrated by Aschner<sup>16</sup>. Briefly, our procedure has been to cut through the soft palate, scrape the mucosa from the sphenoid base, remove the bone with dental burrs and expose the dura, which is then incised, as in hypophysectomy, or a puncture may be made beside the hypophysis, which is clearly visible. A simple apparatus has been devised for giving ether intratracheally.

In general, Aschner's<sup>16</sup> technic was followed. No attempt, however, was made to close the skull defect, except by allowing it to fill with blood and clot. The one case of meningitis occurring in these experiments resulted when a pack was left in the defect to control sinus hemorrhage. The buccal procedure is simpler and requires less preparation and assistance. However, exposure of the hypothalamus is not so good, as the hypophysis practically covers the area sought.

The temporal procedure was devised by Paulesco<sup>17</sup> with Balacesco. It has been used extensively by Cushing<sup>9</sup> and his associates, also by Bell,<sup>18</sup> and recently by Bailey and Bremer<sup>13</sup>. In this, the skin of the head and upper neck is reflected laterally and both temporal muscles separated from their attachments to the cranium. The left zygomatic arch is resected and the subtemporal fossa exposed. A trephine opening over the zygoma root exposes the dura and, slightly enlarged, permits its separation from the skull base to a point where it splits to enclose the gasserian ganglion. Here it is incised 1 cm. horizontally, lateral to the sella. A temporal decompression is then done on the right side and the dura slit in a curve for about 2 cm. Returning to the left side, an elevator is inserted through the dural slit and carefully pushed under the left temporal lobe. This is slightly raised and the hypothalamus exposed.

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15 Marinesco, M. G. *Compt. rend. Soc. de biol.* **4** 509, 1892.

16 Aschner, B. *Arch. f. d. ges. Physiol.* **146** 1, 1912.

17 Paulesco, N. C. *L'hypophyse du cerveau*, Paris, 1908.

18 Bell, B. *The Pituitary*, New York, William Wood & Co., 1919.

In the temporal approach the technic followed was essentially that fully described and illustrated by Crowe, Cushing and Homans<sup>9</sup>. This requires surgical preparation, assistance and more time. It results in a better exposure. However, the important factor of pull on the hypophysis and attached floor of the third ventricle is introduced, when the brain is even slightly tilted. The hypophysis is held fast in the sella by its posterior lobe artery. This, an azygos artery, formed by branches from the two internal carotids (Dandy and Goetsch<sup>19</sup>), pierces the dura of the floor of the sella and enters the posterior part of the posterior lobe. The hypothalamus is securely attached in front by the optic nerves and chiasm. If the "cerebral dislocation" is at all extensive traction must result on the hypothalamus from one of these two fixed points. Hanchett,<sup>14</sup> on an extensive experimental basis, points out that this may be sufficient injury to result in polyuria. No attempt has been made to use the modification of Sweet and Allen,<sup>20</sup> as adopted by Bailey and Bremer,<sup>13</sup> although in this the necessary dislocation is possibly lessened.

Water was supplied in fish bowls securely attached to the side of the cage. The narrow mouth guards against spilling when the bowl is not too full. With older dogs the bowls must be elevated. Urine was collected in covered bowls. In more recent experiments attempts have been made to control evaporation. In the experiments reported at this time the control has not been so careful, and these results are a little high for the water intake and a little low for the urinary output. The combined daily difference, however, is less than 75 c c, which is not so important in a water exchange of over 2 liters.

Specific gravity was determined by weighing daily 25 c c of urine in a weighed, calibrated flask. Weight was calculated to milligrams and the specific gravity at room temperature. Total solids were calculated by the use of Haser's<sup>21</sup> coefficient, as used by Neubauer<sup>22</sup> and also determined by Long<sup>23</sup>. The multiple used for 100m temperature was 0.233.

Urinary chlorids were ordinarily determined after the principle of Mohr<sup>24</sup>. Volhard's<sup>25</sup> method and those used for the blood chlorid were occasionally employed. For blood chlorids the methods of Van Slyke and Donleavy<sup>26</sup> and Rappleye<sup>27</sup> were followed. Sugar, albumin and

19 Dandy, W. E., and Goetsch, E. *Am J Anat* **11** 137, 1911

20 Sweet, J., and Allen, A. R. *Ann Surg* **57** 485, 1913

21 Häser. Quoted by Long and Neubauer

22 Neubauer, C. *Ztschr f anal Chem* **1** 166, 1862

23 Long, J. H. *J Am Chem Soc* **25** 257 and 871, 1903

24 Mohr, L. *Lehrbuch der Titrimethode* **2** 13, 1856

25 Volhard, J. *Ann d Chem u Pharm* **190** 1, 1878

26 Van Slyke, D. D., and Donleavy, J. J. *J Biol Chem* **37** 551, 1919

27 Rappleye, W. C. *J Biol Chem* **35** 509 (Sept) 1918

acetone were sought by ordinary clinical tests. The Folin-McEllroy<sup>28</sup> reagent was used where glycosuria was suspected.

Tissues were fixed in Zenker's solution to which was added instead of glacial acetic acid 10 per cent of neutral solution of formaldehyde. To avoid injury in the removal of the pituitary region, the heads were fixed by perfusion through the carotid arteries, usually for twenty-four hours, until hardening had occurred. The bone of the skull base was then carefully dissected away and the desired block widely removed with the dura intact. A small block consisting of the optic chiasm, hypothalamus, hypophysis and all of the mammillary bodies was then embedded in paraffin and cut serially at 15 microns in sagittal sections. At definite intervals thinner sections were made. In Dog E 14 and Dog I 20 the hypophysis was severed from the hypothalamus and both sectioned serially. Sections were ordinarily stained in hematoxylin and eosin, but use was also made of van Gieson's solution, Mallory's aniline blue stain and Mallory's phosphotungstic acid hematoxylin.

#### PROTOCOLS

Three illustrative protocols of the animals most extensively studied are given. The first presents a typical transient polyuria resulting from buccal puncture of the region in front of the mammillary bodies. This animal was kept under observation for the following six months. No notable changes occurred; there was some gain in weight but estrum occurred normally.

#### REPORT OF PROTOCOLS

EXPERIMENT 1 (Dog E 14) —Was an adult well nourished, white Spitz female, weighing 78 kg. Four day average pre-operative urine was 220 cc. Specific gravity, 1.040, no sugar, acetone or albumin. January 31, buccal exposure, the dura was slit over the hypophysis and puncture of the area in front of the mammillary bodies with discission needle was done. There was no subsequent polynea, dyspnea or motor disturbances. Marked thirst was noticed and polyuria for the first twenty-four hours was 1,000 cc. specific gravity 1.008, albumin +, no sugar or acetone. In thirty-eight hours the excretion of urine was 1,550 cc., which subsided to normal in four days. The average urine excretion for the subsequent five days was 146 cc. Specific gravity, 1.052, no sugar or acetone, traces of albumin. February 9, the dog was back in the enclosure, weighing 72 kg. February 13, 72 kg. February 28, 73 kg. March 5, 79 kg. March 10, 85 kg., with the temperature normal. The weight increase was the only notable change. March 21, 87 kg. March 27, 94 kg. Running with other well fed animals a similar weight gain by another control female was noted. April 2 the weight was 92 kg.

April 14, the animal had been in the metabolism cage for eight days and did not eat well. The average daily water intake was 365 cc., urinary output, 157 cc., specific gravity 1.029, chlorid concentration 0.38 per cent. No sugar or acetone, trace of albumin twice. The dog weighed 95 kg. April 22. Back in enclosure 92 kg. May 14, 90 kg. May 22, 93 kg. June 11, 90 kg., plasma chlorid 0.656 gm. per hundred cubic centimeters.

<sup>28</sup> Folin, O., and McEllroy, W. S. *J. Biol. Chem.* **33**: 513 (March) 1918.



June 20, the dog was in the metabolism cage for four days. There was no polydipsia or polyuria, the weight was 92 kg, rectal temperature, 101, normal chlorid diuresis, 650 c.c. of urine following 5 gm. of sodium chlorid in food, concentration, 1014 per cent. Animal in heat. June 24, 91 kg., 101.0, plasma chlorid, 0.667 gm. per hundred cubic centimeters. Well nourished, in heat. Killed by ether and bleeding.

*Necropsy*—Panniculus 6 mm. thick in mid-abdominal line, moderate omental fat, both kidneys bluish and congested on section, glomeruli prominent. Corpora lutea in both ovaries, fimbriae, oviducts, uterus and vagina enlarged and congested, vulva edematous, 100 c.c. urine in bladder. Hypophysis attached more firmly than normal to sella, normal appearance and size, few surrounding loose fibrous strands. No evident injury to hypothalamus, 6 mm. opening in palate, defect in basisphenoid filled with dense scar tissue, dura thickened and closed.

*Microscopic Examination*—Kidneys moderately congested, bladder normal, ovaries contained normal ova and follicles and early corpora lutea, oviducts and uterus edematous and congested. Increased blood pigment in spleen, other viscera histologically normal. Hypophysis and hypothalamus normal (serial sections). No lesions found in hypothalamus (serial sections).

The second protocol presents a polydipsia and polyuria of four and a half months' duration, an *experimental diabetes insipidus*, subsequent to injury of the hypothalamus through the temporal route. This animal, the most instructive and consequently the most extensively studied, was apparently otherwise normal when sacrificed seven months after operation. The protocol is rather fully abstracted.

EXPERIMENT 2 (Dog F 15)—A brown and white terrier pup, aged 5 months, weighing 65 kg, obtained from dog breeder early in November and kept in animal cages under observation for three months. February 8, in metabolism cage, the dog weighed 92 kg, aged 8 months, rectal temperature, 100.8, four days average preoperative urine 225 c.c., specific gravity, 1.050, no sugar or acetone, trace of albumin, average daily solids 26.39 gm, temperature, 101.1, average water intake 420 c.c., ate all food.

February 12, a temporal exposure of hypothalamus was made, and the brain slightly tilted to the right and a puncture made in the region of infundibulum with a dissection needle. There was no subsequent polypnea or dyspnea. Two hours after operation, the pulse was 192, temperature, 100.2, respiration, 22, and the animal staggered slightly to the right, on walking about room.

February 13, the animal ate all food and ran around, there was no ataxia. Nineteen hours postoperative water intake, 1,460 c.c., urine 940 c.c. No sugar, acetone or albumin in pale, yellow, watery urine. Specific gravity, 1.010. During four hours subsequent to eating the dog drank 1,210 c.c. water, and passed 1,020 c.c. of urine, specific gravity, 1.002. February 14, all the water in the bowl was consumed, 3,000 c.c., so the intake was somewhat restricted. Urine, 2,500 c.c., specific gravity, 1.005, no sugar, albumin or acetone, total solids, 29.13 gm. from February 15 to 20, polyuria declined steadily from 870 to 100 c.c., with a parallel decline of polydipsia. Specific gravity rose to 1.062 and the urine became dark amber. All food was not eaten during this period, and the rectal temperature rose to 103.4. There was some edema of the left side of the face and discharge from the left conjunctiva. The animal gained 0.7 kg. during the first week postoperative. There were no sugar or acetone, some traces of albumin.

The subsequent course of the polyuria, polydipsia, specific gravity, solid output, weight, etc., can best be presented in Figs. 1 and 2. The rectal temperature, observed at times twice daily, remained normal, sugar and acetone were not found except in especially induced conditions, but traces of albumin occurred occasionally. The wound healed uneventfully.

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February 26, increasing polyuria and polydipsia, the animal was very hungry and ate all food, drank 500 cc in about twenty minutes when water was put in the cage. The dog gained 16 kg (3½ pounds) during the last week. February 27, there was a visible increase in weight accompanying the increasing water exchange. The stools were soft. The animal drank 800 cc in four hours during the morning and voided 550 cc, and was very active.

From February 25 to March 4 was a week of maximum polyuria and polydipsia (Table 1). March 3, maximum day, nineteen days postoperative, the

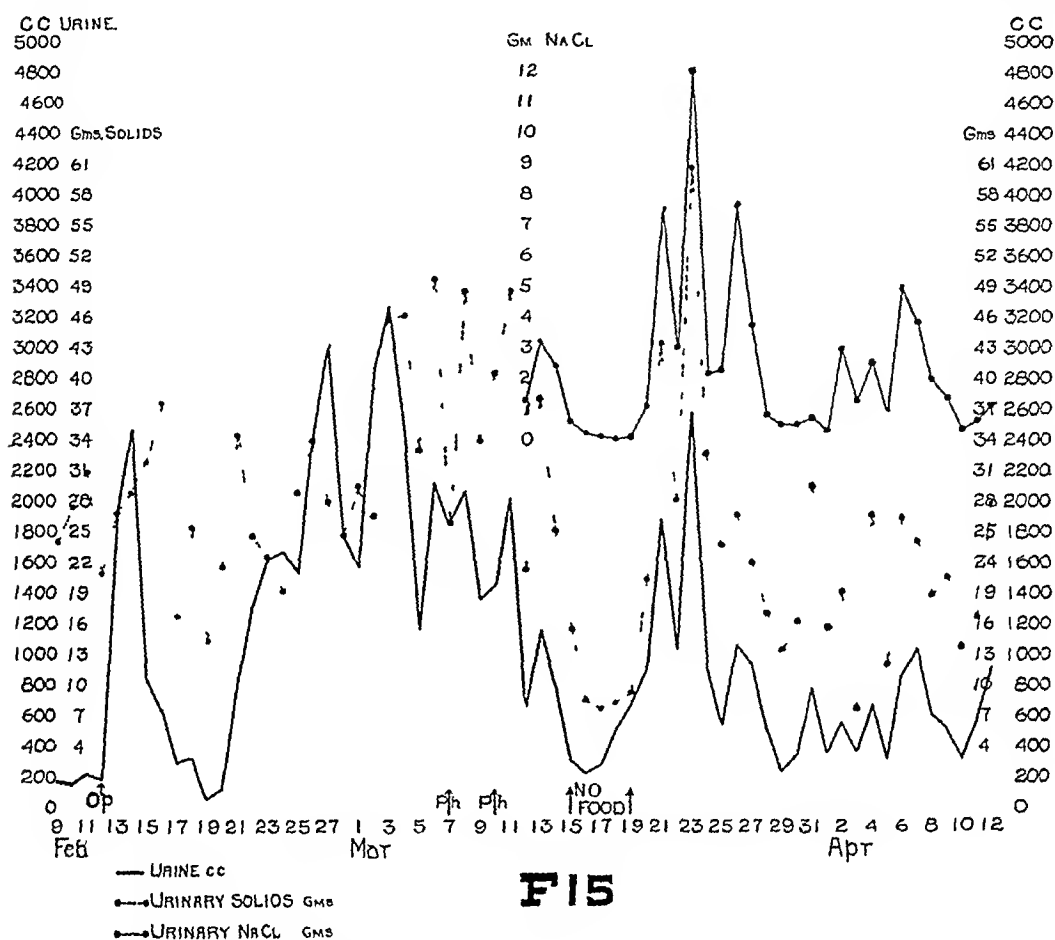


Fig 2—Experimental diabetes insipidus in dog, male, aged 8 months, daily observations

TABLE 1—Week of Maximum Polyuria and Polydipsia Dog F 15

Date	Weight, Kg	Water Intake, C c	Urine Output, C c	Temperature, Rectal	Specific Gravity	Total Solids, Gm	Sugar	Acetone	Albumin
2/25									
2/26	10.8	3,000 (R)	2,450		1.006	34.25	0	0	0
2/26									
2/27		3,800	3,050	102.6	1.004	28.43	0	0	0
2/27									
2/28	11.0	2,300	1,800		1.006	25.16	0	0	0
2/28									
3/1		2,050	1,600		1.008	29.82	0	0	0
3/1									
3/2	11.0	3,550	2,900	102.0	1.004	27.03	0	0	0
3/2									
3/3	11.5	3,700	3,300		1.006	46.13	0	0	0
3/3									
3/4	11.6	3,000 (R)	2,500		1.008	46.60	0	0	0
Averages		3,057	2,514		1.006	32.49			

animal was active and appeared normal save for increasing weight. The first fifteen hour intake was 2,900 cc, urine, 2,100 cc, with a 700 gm increase in weight. Subsequently, from 9 00 a m to 6 00 p m, the dog drank 800 cc water and passed 1,200 cc of urine. No food was eaten during this nine hour interval. The body was full, flanks thick, back broad, the entire appearance was similar to that of an old animal, there was no demonstrable edema. The weight was 11.5 kg.

March 6, evidence of sexual activity, testes firm and not decreasing in size. March 7, phenolphthalein elimination test, normal elimination (Table 2). March 10, second phenolphthalein elimination test, normal elimination. March 12,

TABLE 2—*Phenolsulphonephthalein Elimination Tests Dog F 15*

March 7, 1923	11.1 kg, 101.8, urine of previous 17 hours, 600 cc, 1.014, negative sugar and albumin
10 12 a m	6 mg (1 cc) H W D phenolsulphonephthalein into left lumbar muscles
11 12 a m	No urine voided
12 12 a m	65 cc urine passed, sp gr, 1.014, 47% phenolsulphonephthalein contained 2 hours
2 12 p m	400 cc urine passed, sp gr, 1.005, 36% phenolsulphonephthalein contained 4 hours
4 12 p m	450 cc urine passed, sp gr 1.004, 5% phenolsulphonephthalein contained 6 hours
5 30 p m	350 cc urine passed, sp gr, 1.004, trace phenolsulphonephthalein contained 7 hours
Intake,	2,275 cc, total urine, 1,890 cc, specific gravity, 1.006, total solids, 26.42 gm, temperature, 102, 11.400 gm weight
March 10 1923	11.5 kg, 101.4, urine of previous 19 hours, 765 cc, specific gravity, 1.012, negative sugar and albumin
12 15 p m	6 mg (1 cc) H W D phenolsulphonephthalein into left lumbar muscles
12 55 p m	75 cc urine passed no phenolsulphonephthalein (passed earlier), 1.012 sp gr
1 15 p m	100 cc urine passed, 22% phenolsulphonephthalein contained 1 hour
2 15 p m	75 cc urine passed, 25% phenolsulphonephthalein contained 2 hours
3 15 p m	175 cc urine passed, 29% phenolsulphonephthalein contained 3 hours
4 15 p m	220 cc urine passed, 11% phenolsulphonephthalein contained 4 hours
5 15 p m	90 cc urine passed, trace phenolsulphonephthalein contained 5 hours
Intake,	1,850 cc total urine, 1,500 cc, specific gravity, 1.0117, total solids, 40.98 gm, temperature, 101.5, 11.400 gm weight

beginning of chlorid determinations on urine, as it had been noted that salt meat (ham) definitely increased water exchange. More careful dietary control by weighing started. From March 14 to 19, starvation experiment, no food, free water. Both polydipsia and polyuria lessened (Table 3). March 23, 750 gm salt meat (ham) caused unusual increase in polyuria and polydipsia,

TABLE 3—*Effect of Starvation Dog F 15*

Date	Weight, Kg	Water Intake	Urine Output	Temperature Rectal	Specific Gravity	Total Solids	Sodium Chlorid, per Cent	Sodium Chlorid, Amount	Sugar	Albumin
3/14	11.2			101.0						
3/15	11.2	450	350	101.2	1.02072	16.92	0.220	0.770	0	0
3/15	11.1			101.2						
3/16	11.0	450	270	101.8	1.01469	9.26	0.150	0.405	0	0
3/16	10.9			101.6						
3/17	10.8	550	330	101.6	1.01100	8.48	0.095	0.314	0	Trace
3/17										
3/18	10.8	800	550	101.6	1.00690	8.99	0.045	0.245	0	0
3/18	10.8			101.6						
3/19	10.63	1,150	720	101.6	1.00584	9.81	0.040	0.290	0	0

chlorid and solid output. Concentration of urinary chlorids rose to 0.468 per cent. Increased carbonates in urine. March 26, diminishing hunger.

April 1, 500 gm of meat with 5 gm sodium chlorid, urinary chlorid concentration rose to 0.525 per cent. April 7, variable hunger. April 14, out of cage into enclosure with other animals for one week. Evidence of sexual

activity Weight 11.5 kg April 25, copulated with female in heat, motile spermatozoa demonstrated in smear under microscope From April 29 to May 5, water and fluid restriction with sodium chlorid feeding experiments (Table 4) Urine output fell, could concentrate both solids and chlorids Pre-experi-

TABLE 4—*Effect of Fluid Restriction Dog F 15*

Date	Weight, Kg	Food and Water Intake	Urine Output	Temperature Rectal	Specific Gravity	Total Solids	Sodium Chlorid, per Cent	Sodium Chlorid, Amount, Gm
4/30		350 gm meat						
5/ 1	10.9	400 c c water	350	102.0	1.01529	12.47	0.170	0.595
5/ 1		300 gm meat						
5/ 2	11.0	400 c c water	170	101.8	1.00820	3.25	0.103	0.175
5/ 2		300 gm ham						
5/ 3	11.0	200 c c water	200	101.8	1.04149	19.34	1.146	2.292
5/ 3		5 gm sodium chlorid						
5/ 4	11.0	500 c c milk	210	102.0	1.02522	12.34	1.715	3.602
5/ 4		5 gm sodium chlorid						
5/ 5	11.0	500 c c milk	350	101.4	1.02821	23.00	1.665	5.828
Free Water Supply Resumed								
5/ 5		5 gm sodium chlorid						
5/ 6	10.6	500 c c milk	1,020	102.4	1.01050	24.96	0.617	6.303
		700 c c water						
5/ 6		400 gm meat						
5/ 7	10.9	1,700 c c water	1,520	100.8	1.01327	47.00	0.694	10.550

mental intake averaged 826 c c, and urine, 548 c c for five days. Immediate rise in water exchange followed at the end of the restriction (Table 4).

From May 14 to 17, comparative studies with Dog H 19 and Dog I 20, animals of nearly the same size and weight, on a diet of raw meat, low in chlorids (Table 5). From May 17 to 22, comparative studies on effects of diet, 500 c c

TABLE 5—*Comparative Studies Dog F 15*

Low chlorid diet, 3 days, May 14 to 17, 300 gm lean meat			
	Dog F 15	Dog H 19	Dog I 20
Weight, loss or gain	+0.10 kg	+0.20 kg	+0.10 kg
Average water intake	313 c c	240 c c	210 c c
Average urinary output	273 c c	167 c c	103 c c
Average rectal temperature	101.5	101.6	101.7
Average specific gravity	1.0315	1.0515	1.0489
Average daily solids	19.66 gm	19.51 gm	11.79 gm
Average chlorid concentration	0.280%	0.328%	0.327%
Average daily chlorids	0.822 gm	0.557 gm	0.338 gm
Plasma chlorid	0.682 gm	0.658 gm	0.667 gm
Low chlorid diet, 5 days, May 17 to 22, 500 c c whole milk			
	Dog F 15	Dog H 19	Dog I 20
Weight, loss or gain	—0.60 kg	—0.30 kg	—0.60 kg
Average fluid intake (No. H 20)	500 c c	500 c c	500 c c
Average urinary output	326 c c	228 c c	278 c c
Average rectal temperature	101.2	101.2	101.7
Average specific gravity	1.0154	1.0197	1.0197
Average daily solids	11.92 gm	10.28 gm	12.76 gm
Average chlorid concentration	0.277%	0.388%	0.339%
Average daily chlorids	0.935 gm	0.862 gm	0.964 gm
Plasma chlorid	0.696 gm	0.670 gm	0.688 gm

whole milk, low in chlorids (Table 5). From May 22 to 28, comparative studies, 400 gm cooked meat, high in chlorids (Table 6). From May 28 to June 1 comparative studies, effect of pituitary extract 1 c c daily injected into abdominal wall. Subsequent decrease in polydipsia and polyuria, increase in specific gravity.

TABLE 6—Comparative Studies Dog F 15

High chlorid diet, 6 days, May 22 to 28, 400 gm cooked meat			
	Dog F 15	Dog H 19	Dog I 20
Weight, loss or gain	+0 70 kg	+0 90 kg	+0 80 kg
Average water intake	657 c c	513 c c	375 c c
Average urinary output	535 c c	293 c c	298 c c
Average rectal temperature	101 4	101 5	101 7
Average specific gravity	1 0275	1 0399	1 0461
Average daily solids	30 33 gm	26 31 gm	31 85 gm
Average chlorid concentration	0 722%	1 305%	1,362%
Average daily chlorids	4 176 gm	4 110 gm	4 093 gm
Plasma chlorid	0 705 gm	0 687 gm	0 694 gm
Effect of pituitary extract (1 c c daily, subcutaneously) for 4 days, May 28 to June 1, 400 gm cooked meat			
	Dog F 15	Dog H 19	Dog I 20
Weight, loss or gain	+0 50 kg	+0 30 kg	+0 20 kg
Average water intake	500 c c	480 c c	378 c c
Average urinary output	300 c c	218 c c	205 c c
Average rectal temperature	101 0	100 9	101 4
Average specific gravity	1 0409	1 0455	1 0534
Average daily solids	28 40 gm	22 84 gm	25 24 gm
Average chlorid concentration	0 820%	0 701%	0 918%
Average daily chlorids	2 473 gm	1 454 gm	1 815 gm
Plasma chlorid	0 675 gm	0 636 gm	0 671 gm

and chlorid concentration of urine and lowering of plasma chlorid (Table 6) From June 2 to 3, there was a marked fall in polyuria during two days following pituitary extract, with a rise in the specific gravity and chlorid concentration

June 6, weight 11 6 kg, the dog ate 500 gm of cooked meat, intake 1,000 c c, urine 960 c c, specific gravity 1 02366, total solids 52 92 gm, sodium chlorid total 3 96 gm, sodium chlorid 0 413 per cent, rectal temperature 100 2, no sugar or acetone, albumin +, plasma chlorid 705 mg per hundred cubic centimeters From June 7 to 12, starvation, marked fall in polydipsia and polyuria, increase in specific gravity, temperature normal, acetone present, lowered chlorid output June 29, the weight was 10 6 kg, 400 gm raw meat with 5 gm of sodium chlorid was given Intake 1,100 c c, urine 870 c c, specific gravity 1 01382, total solids 31 24 gm, total chlorids 5 68 gm, sodium chlorid 0 587 per cent, temperature 101 6, plasma chlorid 678 mg per hundred cubic centimeters Increased diuresis over normal and lower concentration of urinary chlorids

July 6, the dog was out of the cage into the enclosure with other animals A slight variable polyuria was still present There was no adiposity or genital atrophy (Fig 3) July 27, in metabolism cage for ten days, weight 10 8 kg, the urine averaged about normal, normal drinking and diuresis after increased protein feeding and giving salt Specific gravity from 1 020 to 1 028, temperature, from 101 6 to 102 6, chlorid concentration from 0 36 to 1 24 per cent No sugar traces of albumin From September 7 to 10, normal intake and output Specific gravity from 1 030 to 1 052, chlorid concentration from 0 793 to 1 196 per cent No sugar, traces of albumin September 12, normal appearance, active and well, weight, 9 6 kg (Fig 4) Killed by ether and bleeding, head perfused with formaldehyd (Zenker's solution)

*Necropsy*—Thin panniculus, moderate amount of omental fat, several nematodes and tapeworms in intestinal tract but no ulcerations the bladder was slightly enlarged but otherwise normal, ureters normal, kidneys bluish, medullary rays prominent, medulla pale, cortex not congested Testes firm, 1 8 cm, bv 2 5 cm, genitalia normal, well developed preputial glands and prostate Liver, spleen, pancreas, suprarenals, lungs, trachea, bronchi, esophagus, intestinal tract and heart normal Thyroids small and firm

Temporal muscles reattached, dural openings closed, dura thickened and adherent to bone defect margins and overlying temporal muscles Brain not adherent to dura Irregular spindle shaped cyst in hypothalamus measuring 2 by 3 by 9 mm, located on the left side, in the region between the optic chiasm,



Fig 3—Experimental diabetes insipidus Dog F 15 at end of diabetes, five months after operation

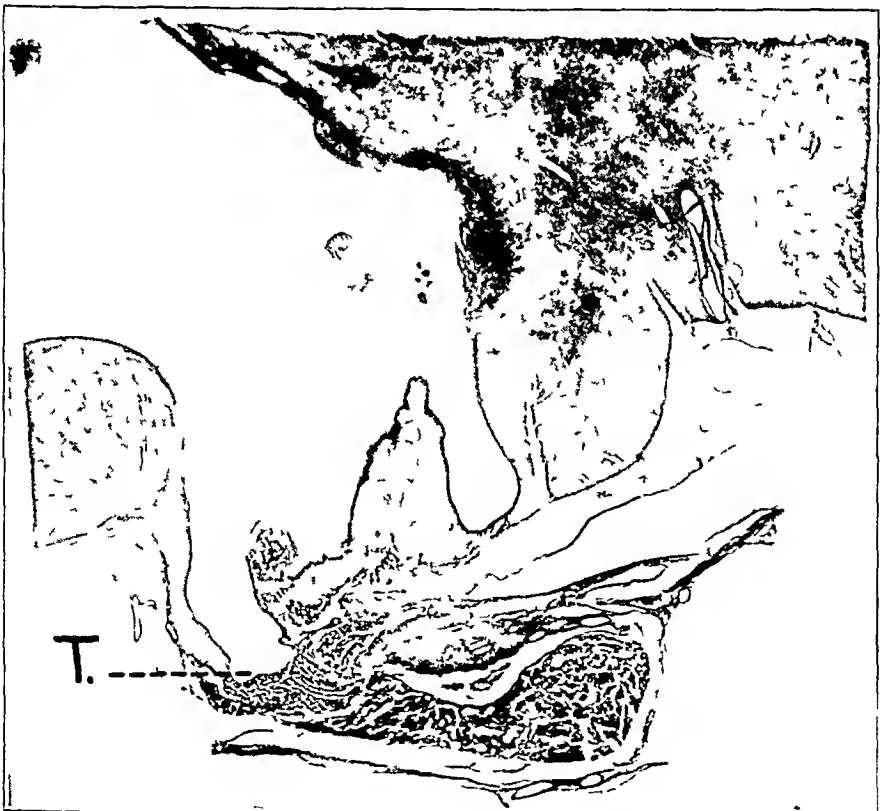


Fig 4—Experimental diabetes insipidus Midsagittal section of hypothalamus and attached hypophysis of Dog F 15 T, defect in floor of third ventricle, closed by pars tuberalis



beginning of the optic tract, pia of the base and the fornix, ahead and to the left of the infundibulum, extending nearly vertically. Hypophysis small, firmly adherent to the sella and surrounded by strands of dense fibrous tissue. Third ventricle dilated inferiorly.

*Microscopic Examination*—Hypophysis surrounded by capsule of fibrous tissue, with some dense interpenetrating strands. Posterior lobe separated from tuber cinereum by dense scar tissue. Pars nervosa atrophic and pressed upward toward the hypothalamus, with condensation of the cellular elements. No demonstrable posterior lobe artery. Normal pars intermedia present on the surface of and about the atrophic posterior lobe. Pars tuberalis histologically normal. Some thick colloid in interlobular cleft (Fig 4).

Cyst in hypothalamus was crossed by many loose fibrous strands, some vascularized. There were numerous large round vacuolated cells in meshes. The wall was slightly thickened, with atrophy of the surrounding nerve cells.

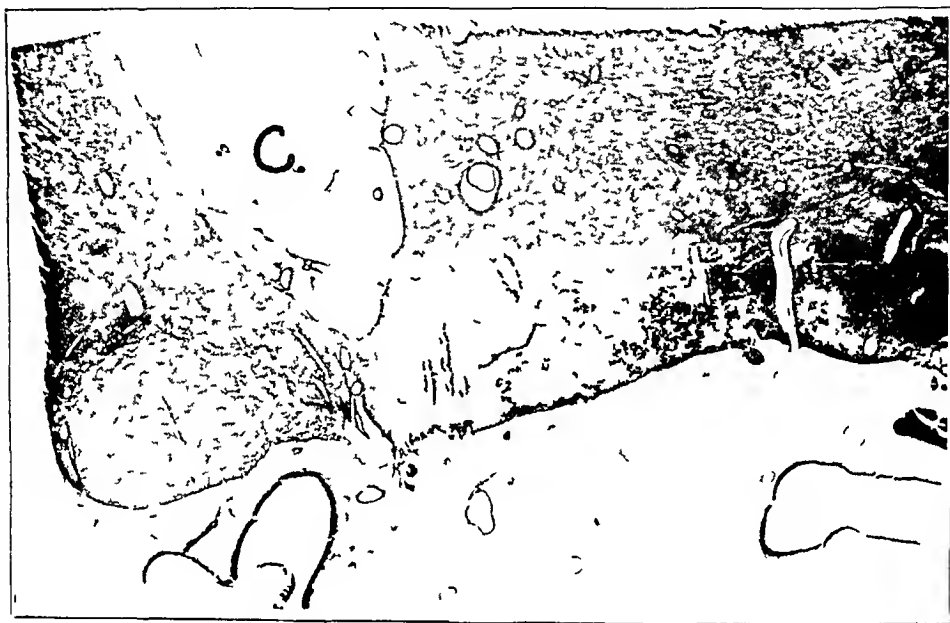


Fig 5—Experimental diabetes insipidus. Sagittal section of left wall of hypothalamus of Dog F 15, presenting the lower part of the cyst found at necropsy. C, cyst cavity.

(Fig 5) Defect in the tuber cinereum just ahead of the infundibulum, with pars tuberalis forming the floor of the third ventricle (Fig 4). Many hyaline bodies in floor and about the enlarged third ventricle.

Testis tubules presented all phases of active spermatogenesis.<sup>79</sup> Spermatozoa in epididymis. Prostate, vas, penis and urethra were normal. The bladder wall was slightly thickened, the kidneys histologically were normal. Thymus remained present, with well developed Hassal's corpuscles. The thyroid contained many small follicles with low epithelium and no colloid, the majority were small and colloid filled, there were a few scattered large colloid filled follicles with hyperplastic walls. No abnormal histology was noted in the liver, suprarenals, parathyroids, pancreas, spleen, heart and pericardium, lymph glands, gallbladder, lungs, bronchi, trachea, submaxillary glands, fundus, pylorus, duodenum, ileum, appendix, colon, cerebellum, pons or midbrain. Cytologic studies have not been made.

The third protocol is that of an animal sacrificed during a polydipsia and polyuria produced by temporal exposure and hypothalamic injury, in order to study especially the histology of the kidney during the disturbance. No changes were found in the kidney save some hyperemia, but the hypothalamus contained a well marked lesion.

EXPERIMENT 3 (Dog 120) -- Adult female, brown and white hound, weighing 9.6 kg. Well nourished, active and healthy. Preoperative comparative studies with Dog 115 and Dog 119 revealed no abnormalities of water exchange. (See Tables 5 and 6 for detailed records.) June 20, in metabolism cage, weight 9.1 kg., rectal temperature, 101.8. June 21 to 26, preoperative control period.

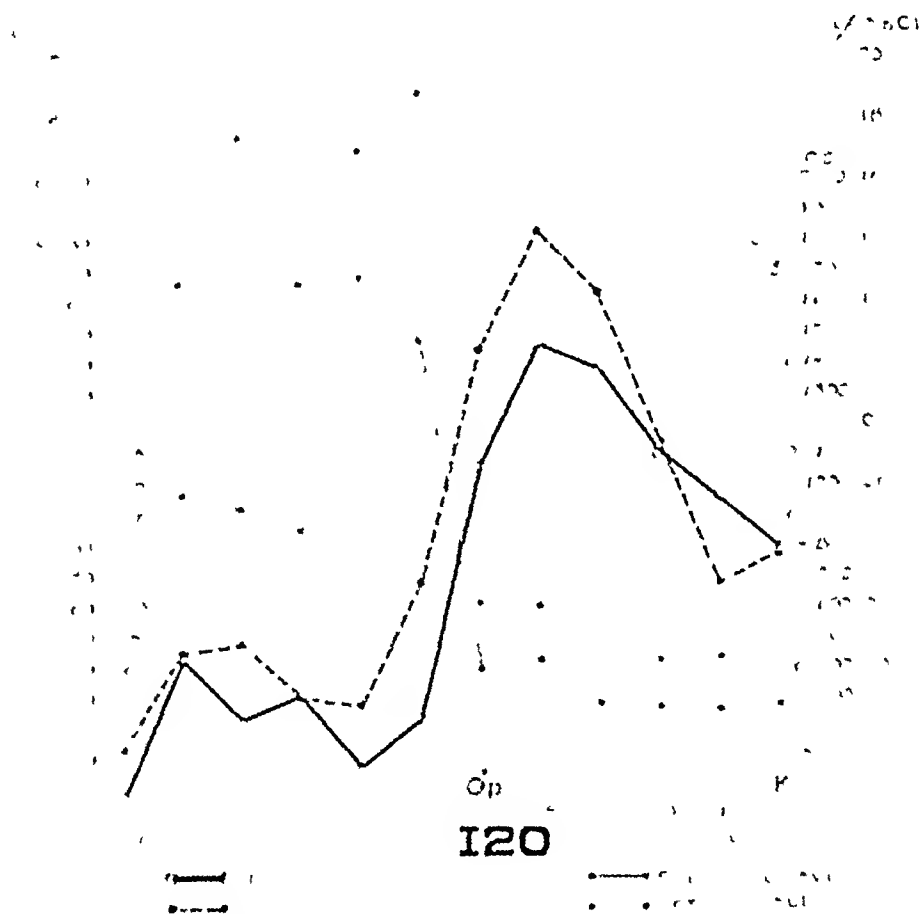


Fig. 6.--Polyuria, adult female dog, daily observations. *Op*, operation, injury to hypothalamus through the temporal route. *A*, killed at end of experiment.

(See Fig. 6 for detail.) Weight 9.6 kg., rectal temperature, 100.8. No sugar, acetone or albumin in urine, etc. all food given. Plasma chlorid was 660 mg. per hundred cubic centimeter.

June 26, a temporal exposure of hypothalamus and puncture in the region of infundibulum were made. There was injury to cerebrum, with hemorrhage, controlled with difficulty. The animal had a tendency to fall to the left after operation. She drank 300 cc. in the subsequent six hours but passed no urine. Three hours after operation the pulse was 128, temperature 101.2 and respirations 20.

June 27, there was edema of the left side of the face, the dog was somewhat comatose, and inclined to fall to the left. Intake greater than output in the morning, the animal did not eat any food. No sugar, albumin +. June 28, there was some spastic paralysis of the left side, especially of the front foot.

The animal ate but little Polydipsia and polyuria, urine pale, watery yellow June 29, there was moderate polyuria and polydipsia (Fig 6) No sugar in urine, temperature, 100.8, purulent conjunctivitis of the right side June 30, the left sided palsy was less marked, weight 7.8 kg, temperature 102.0, the animal ate only a small amount of food July 1, losing weight, taking only a little food July 2, the dog was no longer comatose but active and more alert Weight 7.5 kg, temperature, 102 The animal was killed by ether and bleeding

*Necropsy*—Wound healed, edema of left side of head, mucopurulent discharge from the right eye Moderate panniculus, abundant abdominal fat, slight fatty changes in liver, intestinal tract negative The genitalia were normal, corpora lutea spuria in ovaries The bladder was distended with 200 cc of clear, watery urine, mucosa slightly hyperemic, with several small petechial spots, ureters normal The kidneys were normal, zones and stripes clearly defined, glomeruli prominent, medulla pale The right kidney weighed 22.5 gm, the left kidney, 22.7 gm The thyroids were small and the other viscera negative



Fig 7—Polyuria, adult female dog Sagittal section through the left wall of hypothalamus of Dog I 20 presenting the lesion, L, above and just behind the optic chiasm

The temporal muscles were reattached in scar tissue, not all the sutures were absorbed There was a brown gelatinous exudate between the skin and temporal muscle of the left side The dural openings were closed, the dura was adherent to margins of bone defect, thickened and opaque The dura of skull base was stained dark brown, there was hemorrhage with firm clots about the sella A slight injury to right frontal lobe with hyperemia was noted The hypophysis was surrounded by loose fibrous tissue with some clots There was a firm clot between hypophysis and hypothalamus The hypophysis was served from the hypothalamus and both fixed in formaldehyd (Zenker's solution)

*Microscopic Examination*—The hypophysis was surrounded by young fibrous tissue with some blood clot, organizing a clot between the hypophysis and tuber cinereum posteriorly The posterior lobe and artery were normal There were numerous enlarged follicles, one cystic, in pars intermedia Pars anterior was

slightly compressed. Pars tuberalis was histologically normal. The area of degeneration and softening in the hypothalamus, 2 by 3 by 3 mm, was lying between the chiasm, in the first part of the optic tract, pia of the base and fornix. This was invaded by numerous young capillaries, and the central part was filled with fat loaded phagocytes (Fig. 7).

The ovaries, oviducts, uterus and vagina were normal. There was blood pigment in the uterine mucosa. The kidneys and bladder were moderately congested, there was increased fat in the suprarenal cortex. Irregular dilated cysts in the scattered thymus remained, a slight fatty infiltration about the central veins of the liver lobules was noted. The spleen contained increased blood pigment. The lungs, thyroids, gallbladder, heart, parathyroids and pancreas were histologically normal.

#### EXPERIMENTAL RESULTS AND COMMENT

Thirty-five dogs were operated on in these experiments, twelve by the buccal and twenty-three by the temporal route. The majority of experiments were for the purpose of obtaining familiarity with the technical procedures and their possibilities. These animals were not studied but were subjected to head necropsy soon after operation. The resultant injury to the hypothalamus was especially noted after both total and partial hypophysectomy "cerebral dislocation," as it occurs in the temporal exposure, and lesions by puncture. Sections of the hypothalamus were also made and examined.

The experience gained in this manner has revealed clearly the difficulty of performing any operation on the hypophysis of the dog without some stimulation or even injury of the overlying hypothalamus to which it is attached. An attempt at total hypophysectomy must ordinarily stimulate the tuber cinereum as to it is attached the posterior lobe by its infundibular stalk. Stalk separation, as in posterior lobectomy, causes traction on the floor of the third ventricle, and Hanchett<sup>12</sup> has shown that this consistently results in polyuria. The "cerebral dislocation" if at all extensive, puts undoubted traction on the tuber cinereum through the attachment of the hypophysis to the sella. In this manner it may injure the floor of the third ventricle, or even result in trauma to the hypothalamus behind the attachment of the optic chiasm.

Polyuria was produced six times in eight attempts, twice by the temporal exposure and injury to the hypothalamus, and four times after the buccal route. In two animals no polyuria resulted after buccal puncture. The polyuria lasted for nearly five months in one animal (Experiment 2, Dog F 15), six days in another sacrificed during the polyuria, four days in three and three days in one. It began during the first twenty-four hours in four cases, and during the second day in two. In Experiment 2, the urinary output reached 3,300 cc. It was between 1 and 2 liters in four dogs, and slightly less than 1 liter in one. Five of the animals were adults, the animal on which the best experimental result was obtained was aged 8 months.

## LOCATION OF THE LESIONS

In five of the six animals lesions within the hypothalamus were demonstrated grossly or microscopically. The two most definite lesions are shown in Figures 4, 5 and 7. In one animal, Experiment 1, kept for six months after a transient polyuria following a buccal puncture with a fine needle, no lesion was found. All five were within the optopeduncular area of Camus and Roussy.<sup>7</sup> Three were ahead of the hypophyseal stalk, in that region between the optic chiasm, first part of the optic tract and fornix. Two of these extended well up into the anterolateral wall of the third ventricle. The third was less extensive and resembled that figured by Bailey and Bremer,<sup>13</sup> Plate 2, Dog 14, in location. Two lesions, both grossly demonstrable, were behind the infundibulum and involved the anterior part of the mammillary bodies.

In one of the two animals in which polyuria did not follow buccal puncture, C 9, the puncture had passed behind the mammillary bodies and was demonstrated in the anterior part of the posterior perforated space. In some animals the mammillary bodies are completely overlapped by the hypophysis. Ordinarily, they are just visible behind its posterior margin. In the other animal no lesion was subsequently found.

The lesion in Experiment 2, the animal with experimental diabetes insipidus, was an irregular, well developed, spindle-shaped cyst, lying in the left anterolateral wall of the third ventricle and extending vertically. This may well have resulted from the puncture, with subsequent extensive softening resulting from vascular injury. The absence of a pigmented wall and contained fluid make the probability of a causative local hemorrhage unlikely. However, there was also a tear in the floor of the third ventricle, and the posterior lobe was separated from its attachment and atrophic. In one area, Figure 4 *T*, the pars tuberalis even formed a part of the irregular floor of the dilated third ventricle. Such findings indicated the result of traction on the hypothalamus. It is even possible that the lesion resulting in the cyst occurred in a similar manner.

Serial sections reveal that the region occupied by the cyst is normally supplied by a large artery from the arterial circle, which penetrates the hypothalamus vertically just behind the first part of the optic tract. Injury to this artery with subsequent thrombosis, tearing or even pressure from surrounding clots might well result in infarction with softening and subsequent cyst formation.

In Experiment 3, the lesion is in the same region and resembles an early cerebral infarct. The central portion was packed with large fat-laden phagocytes and there was no hemorrhage. In this animal there were firm clots about the base of the hypothalamus. The shape and extent of the lesion indicates infarction rather than such extensive direct trauma.

## CONTROLS

The buccal operation alone, with opening of the dura of the sellar floor, results in no polyuria. Where the hypophysis herniates with the rush of cerebrospinal fluid the element of traction on the attached tuber cinereum enters and may result in marked polyuria, as in Hanchett's<sup>12</sup> Dog 15. In three animals, however, B 8, L 25 and L 27, no polyuria resulted even after the dura was opened and the hypophysis exposed.

A single temporal operation, with no attempt at cerebral dislocation, resulted in no marked increase of the water exchange. No attempt to perform the temporal operation, with definite cerebral dislocation and no other injury, has been made. Should traction result on the hypophyseal attachment, or on the hypothalamus at its chiasm attachment, or associated vascular injury, polyuria might well result from no other operative injury.

## POLYDIPSIA

In experiments of this nature it appears that the polyuria has received the greater attention.<sup>30</sup> The associated thirst and polydipsia, however, are most striking. Animals observed subsequent to operation not only drank enough water to make up for any operative or anesthetic loss, but actually took enough to increase materially their preoperative weight. Anesthetic alone, or both operations alone with anesthetic, resulted in no such subsequent water intake. Nineteen hours after operation the water intake of Dog F 15 was over 500 c c ahead of the urinary output.

In the curves of Dog F 15 and Dog I 20 the water intake leads, as a rule, the urinary output (Figs 1 and 9). Two animals, weighing 10 kg and 8 kg, respectively, have been observed to drink as much as 500 c c in a relatively short time, more than the average twenty-four hour intake. After operation the observed animals start drinking freely before the polyuria begins.

Recent experiments, not included in this report, give further evidence that thirst is the primary factor. In two cases of polyuria, induced by hypothalamic puncture five and six weeks after previous hypophysectomy, continuous twenty-four hour studies were made subsequent to the operations. The thirst and polydipsia clearly led the ensuing increased urinary output. An account of this animal, M 32, which is still alive, will be reported later.

## RENAL FUNCTION

The freshly passed urine was ordinarily a pale, turbid, watery yellow and faintly acid. The specific gravity fell as low as 1.002, the

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30 Baer, J. *Handb. d. Inn. Med.* 3: 1846, 1918.

concentration of urinary chlorids to 0.035 per cent. During the marked diuresis resulting from a diet high in salt or giving increased sodium chlorid, it became alkaline and contained increased amounts of ammonia and carbonates as well as chlorids. Traces of albumin were found occasionally. However this is a common finding in dogs, especially when they are kept on high protein diets. No glycosuria was found in these experiments, subsequent to operation or during the course of the polyuria. The animals had no food and free water during the twenty-four hours preceding the operation. Acetonuria occurred only during the periods of starvation.

Two separate injections of phenolphthalein, given during a period of high water exchange (Fig. 1), were normally excreted (Table 2). This has also been noted in clinical cases,<sup>31</sup> and in experimental diabetes insipidus in dogs by Bailey and Biemer.<sup>13</sup> According to Marshall and Vickers,<sup>32</sup> in dogs the phenolphthalein is excreted by the convoluted tubules.

No anatomic lesions were found in the kidneys during, soon after or months after the polyuria. Kidneys examined during the polyuria were moderately congested, but otherwise histologically normal. No casts or degenerative changes were found in the tubules. The glomeruli were not notably increased in size. Examination of over fifty sections taken from various parts of both kidneys of Dog F 15 revealed no abnormal histology save a few calcified patches in the renal papillae. These kidneys were examined two months after a polyuria of nearly five months' duration.

During the period of maximum water transport the water intake consistently led the urinary output (Table 1). This was also true in the other polyurias carefully observed. The same condition persists as a rule throughout the polyuria (Figs. 1 and 9). The difference between intake and output was greater than in the preoperative control period, or than in normal control animals. The difference becomes even greater if one considers the water content of the food intake and that of the endogenous metabolism. A part of the increased difference can be accounted for by the weight gain, a part by the loss in the stools, which were occasionally but not constantly soft. It appears, however, that there must be increased water loss elsewhere to account for the discrepancy. As the dog has few sweat glands,<sup>33</sup> this probably occurs from mouth evaporation and an increased loss through the lungs as

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31 Fitz, Reginald. A Case of Diabetes Mellitus, *Arch. Int. Med.* **14**: 706 (Nov.) 1914.

32 Marshall, E. K., Jr., and Vickers, I. L. *Bull. Johns Hopkins Hosp.* **34**: 1 (Jan.) 1923.

33 Ellenberger, W., and Gunther, G. *Vergleichende Histologie der Haus-saugetiere*, Berlin, 1908, p. 189.

expired water. An excess water intake might well leave the body through other avenues than the kidney.

When water was moderately restricted in the animal with experimental diabetes insipidus, the urinary output fell accordingly. As restriction became more severe it fell to 170 c.c., the lowest figure since the low period between the initial and subsequent polyuria of nine weeks previously (Fig. 1). Greater water restriction, accompanied by a diet of salt meat, resulted in a specific gravity of 1.0415 and a urinary chlorid concentration of 1.15 per cent, both the highest since the same period nine weeks previously. There was, however, some solid retention at this time, and consequently complete water deprivation was not attempted. On giving 5 gm. of salt in 500 c.c. of milk the concentration of the urinary chlorid rose to 1.715 per cent, a figure higher than that occurring normally. On resumption of free water supply the water exchange promptly increased, and the intake continued greater than the urinary output (Table 4).

The kidney does not appear to be primarily at fault, as was first held by Meyer<sup>34</sup> in clinical cases of diabetes insipidus. Under enforced conditions, in experimental diabetes insipidus, this organ is able to concentrate both solids and chlorids.

#### THE HYPOPHYSIS

In three of the transient polyurias produced by buccal puncture of the hypothalamus, the hypophysis was histologically normal, as in Dog E 14. In a fourth it was grossly normal but sections were not made. In Dog I 20 the gland was somewhat compressed and surrounding it were clots and some young fibrous tissue. The various parts revealed no marked histologic change save some enlargement of the follicles of the pars intermedia, one of which was cystic. In Dog F 15, also a temporal operation, there was separation of the posterior lobe with atrophy of the pars nervosa. The surrounding pars intermedia was histologically normal and there were many "hyaline bodies" in the base about the third ventricle. No unusual deviations were found in the other divisions.

Pituitary extract given subcutaneously in 1 c.c. doses lowered the water exchange in three animals with polyuria. The result of one injection during the twenty-four hour period was not always definite however, and in one animal it was necessary to give the extract as often as three times daily to obtain a notable decrease. Accompanying the fall in urinary output, there was a rise in the specific gravity and concentration of the urinary chlorids.

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34 Meyer, E. *Deutsch Arch f klin Med* 83 1, 1905



In order to see more clearly the effect of pituitary extract on experimental diabetes insipidus, a comparative study was made on Dog F 15 and two normal control animals of similar size and weight, Dogs H 19 and I 20. This occurred three and one-half months after production of the condition, when the polydipsia and polyuria were not so high as in the earlier experiment. Each animal was given daily 400 gm of cooked meat, free water and 1 c c of pituitary extract subcutaneously just previous to feeding. The results are best presented in Table 6.

The specific gravity, consistently lower than that of the control animals, rose to a more nearly equal level (Tables 5 and 6). The concentration of urinary chlorids, previously lower than that of both controls rose to equal their average. The plasma chlorid, consistently higher on several previous determinations fell to the lowest value observed in Dog F 15 up to that time.

Camus and Roussy found that injection of pituitary extract had no specific effect on the permanent polyuria produced in their dogs. Bailey and Bremer, however, show (Fig 5) that the output falls and the delta rises when repeated small doses are employed. No mention is made of the change in the accompanying polydipsia.

The effect of pituitary extract in decreasing the polyuria of diabetes insipidus is commonly regarded as a result of its action on the kidney, or on the renal blood flow. In a case seen recently with Hall, which has been previously reported,<sup>35</sup> the thirst was a striking feature. On one occasion the patient was observed to drink over 1,200 c c of water in a few minutes, and a polyuria shortly ensued. The patient stated that amelioration of the thirst occurred relatively soon after the subcutaneous injection of pituitary extract. Studies on Dog F 15, a case of experimental diabetes insipidus, indicate that thirst and polydipsia are primary factors in the disturbance. Consequently it seems reasonable to ask if the effect of pituitary extract may not in some way be connected with the thirst mechanism. A suggestion in this connection is offered by the finding that the blood chlorid was lowered after injection of the extract subcutaneously.

#### OTHER ORGANS

In Dog I 20 the mucosa of the urinary bladder was hyperemic and presented several petechial spots. The ureters were normal. This animal, even previous to operation, would not urinate in the metabolism cage until the bladder was considerably distended. During the polyuria there probably resulted even more marked distention, and 200 c c of urine was found in the bladder at necropsy. In an animal of approximately the same weight, observations of the polyuria were made during a continuous twenty-four hour period. The successive single urinations

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35 Hall, G W. *Am J M Sc* 165 551 (April) 1923

were consistently close to 135 c c. Possibly there was some thickening of the bladder wall of Dog F 15, but no other changes in the urinary tract.

No changes were observed in the gonads or genitalia, subsequent to operation followed by polyuria. Four animals were females and two males. Only three animals, however, were kept for any extensive period after operation. In Dog E 14 necropsy revealed the anatomic changes of estrum. In the one animal which developed meningitis following operation, but which had no polyuria, definite degenerative changes were found in the spermatogenic epithelium.

The thyroids of Dog F 15 were smaller and firmer than normal. Histologically, they represent a phase in the return to the colloid or resting state after a previous hyperplasia (Marine<sup>36</sup>). Bensley<sup>37</sup> has pointed out that this is of no great significance as the amount of iodine intake was not known, or the amount of meat eaten during the last six weeks of the animal's life.

No other changes were found in the viscera of five animals examined both grossly and microscopically which could be interpreted as resulting from the disturbance. The endocrine organs were especially examined.

#### CHLORIDS

In the daily fluctuations of the early polyuria of Dog F 15, it was noted that the water exchange became noticeably greater on those days that the animal was fed salt meat. Bailey and Bremer<sup>13</sup> have already noted this polyuric action of sodium chloride in one of their dogs shown to have an experimental diabetes insipidus (Table 2, Dog 10). The unusually high diuresis occurring after giving salt in clinical cases of diabetes insipidus is well known. Consequently, studies were made on the urinary chlorids, the effect of giving salt and diets low and high in chlorids and on the blood chloride.

In Dog F 15 the concentration of urinary chlorids, like the specific gravity, remained ordinarily lower than normal (Fig. 1, Tables 5 and 6). It rose on giving salt or high chloride diets, but with free water supply available, the figures remained still somewhat below normal (Table 6). It fell definitely on starvation, the same as in normal control animals, as in this manner the body protects itself from chloride loss. Water restriction alone, or combined with giving sodium chloride, raised the concentration to normal (Table 4). Under enforced conditions the kidney is apparently able to concentrate chlorids. In this, these findings confirm those of Bailey and Bremer<sup>13</sup> in their Dog 10. There is also a

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36 Marine, David. The Importance of Our Knowledge of Thyroid Physiology in the Control of Thyroid Disease, *Arch. Int. Med.* **32**: 811 (Dec.) 1923.

37 Bensley, R. R. *Am. J. Anat.* **19**: 57 (Jan.) 1916.

marked drop in the concentration at the acute onset of the polyuria in Dog I 20 (Fig 9)

The blood chlorid of Dog F 15, determined repeatedly during the last six weeks of the diabetes, was found consistently higher than that of normal animals. This was also true in comparison to normal control animals on similar regimens (Tables 5 and 6). It fell from an average of 701 mg per hundred cubic centimeters in five previous determinations to 675 mg per hundred cubic centimeters after repeated daily injections of pituitary extract (Table 6). This was the lowest figure observed. It was also lower at the end of the polyuria and polydipsia, 678 mg, and was 675 mg at the end of the experiment.

This finding of an hyperchloremia, during the latter part of an experimental diabetes insipidus, is in accord with certain clinical findings already reported by Veil,<sup>38</sup> who describes an hyperchloremic form. The same has been noted clinically by Meyer and Meyer-Bisch.<sup>39</sup> The hyperchloremia of Dog F 15 may have been a manifestation of blood concentration. Accompanying studies on the blood urea, sugar, specific gravity and hemoglobin were not made to determine this possibility. The relation of the finding to the phenomenon of thirst may possibly throw some light on the nature of experimental diabetes insipidus as here produced.

Occasionally, during the course of the experimental diabetes insipidus, a sudden marked accentuation of the polyuria occurred without apparent cause. At such times unusually large amounts of chlorids were passed at a moderately high concentration. The turbid urine became alkaline and contained also an increased amount of carbonates. The same phenomenon occurred after giving a diet high in chlorids (March 23, Figs 1 and 2), and on giving increased amounts of salt (Table 4). That the sudden diuresis was possibly due to polydipsia beyond a certain point in a salt charged blood stream is indicated by the work of Haldane and Baird.<sup>40</sup>

#### DIET

Changes in the diet supplied had an effect on the polyuria and polydipsia, more marked, however, if there was a corresponding increase in the contained chlorids. Diets high in protein and chlorids resulted in the most marked polyuria (salt cooked meat, Table 6). Those lower in protein, and especially in salt, lowered the output in both normal and polyuric animals (raw meat, Table 5). Diets high in protein but low

38 Veil, W. H. *Biochem Ztschr* **91** 317, 1918.

39 Meyer, E., and Meyer-Bisch, R. *Deutsch Arch f klin Med* **137** 225, 1922, *Ztschr f klin Med* **96** 469 (Feb) 1923.

40 Haldane, J. B. S., and Baird, M. M. *J Physiol* **56** 259 (May) 1922.

in salt (raw meat) resulted in a somewhat greater accentuation than those high in carbohydrate but low in salt (bread and milk)

Starvation definitely decreased both the polydipsia and polyuria (Fig 1, Table 3) The specific gravity remained low, but the total solid output fell The amount and concentration of the urinary chlorids fell There was, however, after an early decrease, an increasing water exchange at the end of the experiment In a second five day starvation period on Dog F 15 and two normal control animals, an even more marked decrease of the water exchange occurred Bailey and Bremer,<sup>13</sup> on the contrary, found that deprivation of food had no appreciable influence No details of the time or duration of their experiments are given

The polyuria and polydipsia occurring in Dog I 20 (Fig 9) is low Two reasons may account for this that the diet was largely bread moistened with milk and that the animal ate but little of the food supplied

#### ASSOCIATED CONDITIONS

The temperature ordinarily fell during the operation and was low immediately after, returning to normal relatively soon after recovery from the anesthetic During recovery it usually rose moderately, especially after the temporal procedures No hypothermia, save that occurring during operation if the dog was not kept warm, was observed after puncture Also no hyperthermia has been noted subsequent to hypothalamic injury During the height of water exchange no variations were noted outside of the normal range

In the case of experimental diabetes insipidus, following the initial polyuria, a sudden fall in the water exchange occurred (Fig 1). During this time the food was not all eaten and the temperature rose to 103.6, subsequent to the operative procedure There was no demonstrable infection In clinical cases fever consistently lowers the polyuria (Baer<sup>30</sup>) No other temperature variations outside the normal range were noted throughout the experiment

#### ADIPOSOGENITAL DYSTROPHY

The frequent association of polyuria and polydipsia with that syndrome in which adiposity accompanies genital atrophy is recognized both clinically and experimentally Lewis and Matthews<sup>41</sup> state that polyuria is associated with 7 per cent of the cases of Frohlich's syndrome In the animal in which Cushing<sup>9</sup> and his associates first demonstrated experimental adiposogenital dystrophy, there was a polyuria of from 675 c c to 2,400 c c lasting for six months (Observation

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41 Lewis, D, and Matthews, S A Tr Chicago Path Soc 9:16, 1913

34) In a second animal there was a lesser polyuria of three and a half months duration (Observation 55)

Camus and Roussy<sup>42</sup> have also found that their animals with permanent polyuria may develop adiposogenital dystrophy Two of the three permanent polyurias produced by Bailey and Bremer also developed this syndrome (Dogs 10 and 22)

No adiposity accompanied by genital atrophy was observed in any of the experiments reported at this time Only three of the animals, however, were kept under observation for any length of time following the operation There was some weight gain in Dog E 14 during the subsequent six months but the animal was well fed and cared for Estrum occurred normally and the ovaries were histologically normal

Dog F 15, an 8 month growing animal, gained rapidly and visibly in weight during the early increasing water exchange until he resembled an old dog There was no demonstrable edema The definite weight gain paralleled an increasing water intake The appearance, and more slowly the weight, returned to the preoperative condition as the polyuria and polydipsia subsided During the last two months there was no adiposity

During the diabetes in Dog F 15, there was sexual capacity demonstrated At one time motile spermatozoa were observed in a microscopic preparation made after copulation The female kept under observation in a metabolism cage during estrum, the time of copulation and the first part of pregnancy, delivered seven normal, healthy pups, five male and two female, about two months later It is of interest to record that none of them had a polyuria, when studied in metabolism cages over periods of at least one week Sections of the testis, made at the end of the experiment, were histologically normal and active spermatogenesis was demonstrable

This animal appears to be a case of experimental diabetes insipidus, uncomplicated by adiposity or genital atrophy The main lesion in the hypothalamus is clearly in the anterior part of the optopeduncular area The tuber lesion is also ahead of the pituitary stalk The sudden increase in water intake beginning ten days after the operation, with a notable increase in weight and accompanying obese appearance of the animal during the subsequent two weeks, suggest an acute relationship between water balance and the obesity There was no other evidence of an experimental Frohlich's syndrome

Ordinarily, the weight fluctuates somewhat, depending on the daily balance between intake and output No weight loss subsequent to dehydration by excessive output was noted

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42 Camus, J, and Roussy, G Rev neurol 27 1113, 1920

## SUMMARY

*Production*—By injury of the hypothalamus in the region of the pituitary stalk it was possible to produce, among several transient polyurias, one of long duration. An extensive daily study of this case has shown that it corresponds to certain cases of diabetes insipidus occurring clinically, more especially to those regarded as primary or functional polydipsias. In the one case, Dog F 15, which may fairly be called an experimental diabetes insipidus, the water exchange was apparently lowered by fever, and definitely so by starvation. Phenolphthalein elimination was normal. High protein diets, those containing considerable protein and salt, and salt added to all diets clearly increased the water exchange. The chlorids were especially polyuric.

Under enforced conditions, water and fluid restriction with salt feeding, the kidney was able to concentrate both solids and chlorids. The blood chlorid was found consistently higher than normal in this dog, and higher than that of normal dogs on similar regimens. Pituitary extract given subcutaneously decreased the water exchange, increased both the solid and chlorid concentration of the urine and lowered the higher blood chlorid.

There was an early noticeable increase in weight during the early increasing water exchange, with an obese appearance. This disappeared as the water intake and output returned to normal. There was no evidence of genital atrophy. Necropsy of this animal revealed a small cyst in the hypothalamus, near the infundibulum. There was also a tear in the floor of the third ventricle in front of the pituitary stalk, and the pars nervosa was separated and atrophic. The kidneys and testes were histologically normal.

In this animal an uncomplicated case of experimental diabetes insipidus had apparently been produced, with an accompanying well marked lesion of the hypothalamus.

*Pathogenesis*—The rôle played by the hypophysis in five transient polyurias and one of long duration is by no means clear. In the animal with experimental diabetes insipidus there was separation and atrophy of the pars nervosa, but the remaining parts were histologically normal. No changes were found in four hypophyses, a fifth was compressed and there were enlarged follicles in the pars intermedia.

The recent isolation by Abel<sup>43</sup> of the extremely potent pituitary tartrate, and the subsequent study of its effects<sup>44</sup> on animals and man make it even more difficult to rule out completely the hypophysis from

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43 Abel, J. J., Rouiller, C. A., and Geiling, E. *J. Pharmacol. & Exper. Therap.* 22: 289 (Nov.) 1923.

44 Abel, J. J., and Geiling, E. *J. Pharmacol. & Exper. Therap.* 22: 317 (Nov.) 1923.

the observed disturbances of the water balance Pituitary extract subcutaneously nearly restored the normal condition in Dog F 15

The hypothalamus, however, is clearly involved in five of the six polyurias The lesions of Dogs F 15 and I 20 are striking and undoubtedly led to irritation of surrounding regions In Dog F 15 the irritation must have been of long duration Because of the extent and location of the lesion it seems probable that Dog I 20 would have developed a permanent polyuria had the dog not been sacrificed

These experiments lead to the conclusion that the pathogenesis of the condition is in the hypothalamus, although the part played by the hypophysis in the disturbance is not clear Recent experiments, on animals still living, have added more evidence to this view Confirming the observations of Camus and Roussy<sup>7</sup> and Houssay,<sup>45</sup> it has been possible to produce polyuria twice in an animal after hypophysectomy (Dog M 32) The results thus far are in accord with those of Camus and Roussy, Houssay, Hanchett, and Bailey and Bremer, in that the disturbance is regarded as essentially a phenomenon of the hypothalamus

*Nature*—The nature of the disturbance is not clear Further metabolic studies of the cases of permanent polyuria, which may be readily produced, should add continuously to the solution of this problem From the work thus far, two factors stand out as deserving of further consideration, the pronounced thirst and the relations of the chlorids

The evidence leading to the view that thirst and polydipsia be regarded as primary has been presented There is ample evidence to warrant such a position It seems, from this study at least, as reasonable to regard experimental diabetes insipidus as an hypothalamic thirst phenomenon as to regard it as being a primary pituitary polyuria

The polyuric action of the chlorids, the increased blood chlorid becoming lower as the polydipsia and polyuria lessened after pituitary extract, and the changes in concentration of the urinary chlorids after pituitary extract suggest that the chlorids play more than a passive part in the disturbance It may be that this is in relation to the thirst mechanism

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<sup>45</sup> Houssay, B A , Carulla, J E , and Romana, S Rev Soc med arg, Jan-March, 1921

# THE ASSOCIATION OF ACHYLIA AND ANEMIA OF DIFFERENT TYPES IN THREE MEMBERS OF THE SAME FAMILY, AND THE BEHAVIOR OF THE COLOR INDEX IN PERNICIOUS ANEMIA<sup>\*</sup>

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As shown in a previous paper simple anemia is a frequent finding in cases of gastric achylia. If one were to assume that achylia is of pathogenic importance in the production of this anemia or of pernicious anemia, the question would arise why achylia should cause simple anemia in some cases and pernicious anemia in others.

Recently, evidence has been presented which suggests that pernicious anemia develops on the basis of some hereditary predisposition.

In particular Schauman<sup>1</sup> and Martius have supported this view. A review of the known facts concerning the inheritance of pernicious anemia has recently been published by Meulengracht<sup>2</sup>. In this connection it is interesting to note that we have observed both types of anemia associated with achylia in the same family.

## DIFFERENT TYPES OF ANEMIA WITH ACHYLIA IN ONE FAMILY

The following observations concern three patients with achylia of whom two, father and son, died of pernicious anemia, while a third, the daughter showed a pronounced relapsing microcytic anemia.

The histories and blood findings in these patients are detailed at the end of the paper.

It would seem reasonable to assume a connection between the achylia and the anemia in these cases. In Case 1 (pernicious anemia) achylia was demonstrated before the onset of anemia, and the history of gastrointestinal trouble in Case 2 (pernicious anemia) makes it probable that in this patient also it antedated the anemia, although, as no test meal had been taken prior to admission, this was not positively demonstrated.

In Case 3 (chloroanemia) a miscarriage had evidently aggravated the anemia, but the anemia had been present before the miscarriage and the patient suffered two relapses after successful iron treatment, which would not have been the case if she had had a simple anemia due to hemorrhage. Curiously enough, this third case showed the typical glossitis which Hunter described as characteristic of pernicious anemia.

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<sup>\*</sup> From the medical clinic of the University of Copenhagen.

1 Schauman, O. *Deutsche med Wchnschr* 26, 1910.

2 Meulengracht, E. *Folia haematol* 28 217, 1923.



The circumstance that both pernicious and simple anemia are found associated with achylia even within the same family raises the question whether transitional forms of anemia may occur

It must be admitted that the difference between the two types is clear-cut, and that one does not see simple anemia with achylia develop into the pernicious type. The simple anemia with achylia described in our former paper is chronic and liable to relapse, but does not threaten the life of the patient and has a clinical picture of its own. The main difference between pernicious and simple anemia is that the first shows the picture of a hemolytic anemia, the second does not. If we assume that the achylia (or its intestinal consequences) is a causative factor, at least it appears that the response in the blood is different in the two types of anemia.

The difference between the two types of anemia is the behavior of the color index. This is generally considered quite significant in the differential diagnosis. We have, however, observed at least one case which is evidence against the invariable validity of the index in the differentiation.

#### PERNICIOUS ANEMIA WITH AN ATYPICAL REMISSION

The increase of index beyond 1, i. e., an average megalocytosis, is well recognized to be one of the most characteristic changes of pernicious anemia. In opposition to the opinion of the German school we believe that the absence of megaloblasts does not weigh greatly against the diagnosis of pernicious anemia, since they may be difficult or impossible to find during long periods of the disease.

As to the behavior of the index during remissions opinions vary.

Thus Naegeli<sup>3</sup> writes

"even in this stage (i. e., remission) the index remains high. I have only seen normocytosis with low color index, where there was not a remission, but incipient recovery in cases with known etiology."

Zadek<sup>4</sup> has described four cases of typical pernicious anemia when the remission was less than 1.

Also a case of this sort has recently been published by Willebrandt<sup>5</sup>. His case, however, was peculiar as there was no achylia and after ten years the patient was still living with a normal index, which would seem to bear out Naegeli's statement.

Our case, the history and findings of which are detailed at the end of this paper, was a typical idiopathic pernicious anemia, which during a remission and part of a relapse changed type, so that it resembled in nearly all respects a simple anemia. The further course was classic, the patient was readmitted with a typical high index and all other signs of

3 Blutkrankheiten und Blutdiagnostik, Berlin-Leipzig, 1920

4 Zadek, T. Munchen med Wchnschr 68 1346 (Oct) 1921

5 Willebrandt, E. A. Acta med Scand 56 419, 1922

pernicious anemia and died in the hospital. At the beginning and end the picture was the classical one of pernicious anemia, while an observer seeing the patient for the first time between February and May, 1920, would probably have made a diagnosis of simple anemia with the correspondingly favorable prognosis. The few rather large cells would probably not have been noted if the previous history had not led to a careful search for them. A measurement of the diameter of a large number of red cells might have helped, while a determination of the average diameter would have availed as little as the determination of the average volume, which is the essence of the index determination. This case serves as a warning against relying absolutely on the color index, even if this in the great majority of the cases is the best diagnostic sign of pernicious anemia. This led us to make a short statistical summary of the behavior of the index in various stages of pernicious anemia.

#### BEHAVIOR OF THE COLOR INDEX IN VARIOUS STAGES OF PERNICIOUS ANEMIA

Our material consists of fifty-four cases, of which one has been admitted four times and eight twice (sixty-five admissions in all). In presenting these we select the following examinations:

1 *Color Index at Time of Admission*—Patients generally very ill and declining.

2 *Color Index at Height of Remission*—The examination showing the highest hemoglobin percentage observed, either just before the discharge or before relapse set in (only in cases showing distinct improvement).

3 *Color Index Just Before Discharge in Unimproved or Deteriorated Condition*

4 *Color Index Just Before Death in the Hospital*

TABLE 1—*Color Indexes*

Color Index	Maximum	Minimum	Average	Per Cent Greater than 1.15	Per Cent 1.15 to 0.85	Per Cent Less than 0.85
At time of admission, sixty-five examinations	2.1	1.05	1.45	91	9	0
At time of remission, thirty-four examinations	1.9	0.8	1.3	76	21	3
Before discharge in unimproved or deteriorated condition, nine examinations	1.9	1.35	1.6	100		
Just before death, twenty-six examinations	2.15	0.9	1.5	88	12	0

According to this analysis it seems evident that the color index is generally lower during remissions than at any other stage of the disease. A normal index, however, is met with in barely one-fourth of the remissions. Also we note that two of these remissions with normal index proved to be persistent, so that renewed examinations after several years failed to disclose the slightest trace of the disease.

### THREE CASES OF ACHYLIA WITH ANEMIA OF DIFFERENT TYPE IN THE SAME FAMILY

CASE 1—The father died some years ago, aged 67. Several examinations disclosed that he had complete achylia, and the hemoglobin dropped to 30 per cent before death. The skin was yellowish. Stained blood films showed changes typical of pernicious anemia. He was not treated in any hospital.

CASE 2—The second patient, when first observed, was aged 44, and was a son of the previous patient (Case 1). For fourteen years he had suffered from periodic diarrhea. In 1919 he became weak and easily tired and was admitted to the clinic in May.

Physical examinations showed pronounced pallor with a yellowish tint but no other changes. Ewald test meal gave 15 cc of poorly chymified gastric contents. Congo red, none, phenolphthalein, 11.

Under treatment the patient improved rapidly and was discharged. He felt well for some time, but was readmitted in April, 1920, in a very anemic condition. From this time the patient's condition steadily deteriorated in spite of transfusion and other treatment. He died August 1. Necropsy showed anemia and hyperplasia of the spleen.

TABLE 2—*Blood Examination*

Date	Hemo- globin, per Cent	Red Blood Cells, Millions per O Mm	Index	Leuko- cytes per O Mm	Plasma Color	Platelet Count	Blood Films
First admission, 1919							
5/31	55	1.87	1.5	3,500	} Markedly yellow	116,000	} Anisopoikilomegalocytosis, normoblasts and megalo- blasts, later some poly- chromatophilic reds
6/7	53	1.65	1.6	2,900		108,000	
6/14	59	1.90	1.55	2,600		90,000	
6/21	66	2.02	1.65	4,600		173,000	
6/28	77	2.49	1.5	4,800		177,000	
7/7	86	2.69	1.6			263,000	
Second admission, 1920							
3/18	68	2.46	1.4	3,100	11	107,000	
3/30	63	2.12	1.5	3,800	12	81,000	
4/15	61	1.93	1.6	3,700	8	82,000	
4/26	67	2.20	1.5	4,500	12	83,000	
5/4	62	2.20	1.4	3,600	8	83,000	
5/17	57	2.03	1.4	3,300	7	62,000	
6/18	42	1.50	1.4	1,900		29,000	
6/28	29	1.24	1.2	1,900			
7/12	22	0.90	1.2	1,600			
7/19	26	1.10	1.2	1,400			
7/26	19	0.82	1.2	1,100			

CASE 3—The third patient was a daughter of the first patient and sister of the second patient (Cases 1 and 2). At the time of the observation she was aged 43. She was admitted Dec 31, 1919, and discharged March 30, 1920.

The patient had had nine children and had miscarried twice. She had suffered some loss of blood at the last miscarriage in 1916. The menstruation had been regular, except for pregnancies, and never was profuse. As a young girl she had suffered from "chlorosis" and had been treated with iron. In the six years before admission the patient had been pale and easily tired. After the last miscarriage she had been treated for anemia in another hospital, the hemoglobin mounting from 42 to 70 per cent (Sahli). The pallor and lassitude soon returned, however, and became aggravated during the six months before admission. She complained of burning and tenderness of the upper surface of the tongue.

Physical examination showed nothing but extreme pallor without any trace of jaundice.

Ewald test meal repeatedly gave only a few cubic centimeters of poorly chymified gastric contents showing no reaction to Congo red, and phenolphthalein. 10. The feces contained no blood.

The anemia proved refractory until large doses of reduced iron were given. Immediately following this treatment the hemoglobin began to mount, and the patient was discharged March 30, 1920, in good condition. From personal communications we know that later she had another relapse of the anemia which also reacted favorably to iron.

TABLE 3—*Blood Examination*

Date	Hemo- globin, per Cent	Red Blood Cells, Millions per C Mm	Index	Leuko- cytes per C Mm	Plasma Color	Platelet Count	Blood Films
1/ 6	34	3.64	0.5	2,500	1	347,000	Anisopoikilomicrocytosis, relative lymphocytosis, the changes gradually decline in intensity
1/17	34	3.37	0.5	3,000	1	381,000	
2/10	38	3.53	0.5	4,000	1	339,000	
2/24	40	3.69	0.5	5,200	1	394,000	
3/ 9	58	4.32	0.7	4,200	1	362,000	
3/23	77	4.76	0.8	4,200	1	324,000	
3/30	82	4.95	0.8	5,200	1		

TABLE 4—*Blood Examination*

Date	Hemo- globin, per Cent	Red Blood Cells, Millions per C Mm	Index	Leuko- cytes per C Mm	Plasma Color	Platelet Count	Blood Films
First admission							
12/ 3/19	36	1.41	1.3	1,000	6	73,000	Anisopoikilomegalocytosis, several megaloblasts and normoblasts and poly- chromatophilic reds
12/22/19	26	1.07	1.2	3,400	5	58,000	Anisopoikilomegalocytosis, several megaloblasts and normoblasts and poly- chromatophilic reds
1/ 5/20	45	1.44	1.35	3,100	3	344,000	Anisopoikilomegalocytosis, several megaloblasts and normoblasts and poly- chromatophilic reds
1/12/20	57	2.11	1.4	1,500	5	457,000	As before, but only few nu- cleated reds
1/26/20	59	3.02	1.0	3,000	2	757,000	Prevalent microcytosis, no nucleated reds, no certain megaloeytes
2/ 9/20	66	4.03	0.8	6,200	3	408,000	Prevalent microcytosis, no nucleated reds, no certain megaloeytes
2/23/20	72	4.50	0.8	5,000	2	700,000	
3/ 1/20	71	4.86	0.7	5,000	2	383,000	Prevalent microcytosis, no nucleated reds, no certain megaloeytes
3/ 8/20	75	4.72	0.8	4,100	2	362,000	Prevalent microcytosis, a very few larger cells
3/16/20	73	4.18	0.9	3,000	2	415,000	
In another hospital							
5/ 1/20	41	2.47	0.8	2,700	4	85,000	Anisopoikilocytosis, several megaloeytes, but prevalent microcytosis
Second admission							
12/ 3/20	21	0.78	1.3	3,500	8	3,000	Anisopoikilomegalocytosis, several megaloblasts
12/ 9/20	26	0.85	1.5				
12/17/20	24	0.58	2.0	3,400			
1/ 5/21	21	0.49	2.1	3,000			
Differential Count							
	12/22/19	5/1/20	12/17/20				
Neutrophil	58	76	66				
Eosinophil	2	0	1				
Basophil	0	1	0				
Monoeytes	1	2	1				
Lymphocytes	39	21	32				

## A CASE OF PERNICIOUS ANEMIA WITH ATYPICAL REMISSION

CASE 4—The patient at the time of the first admission (Dec 2, 1919) was a married woman, aged 49. For a few months before admission she had suffered from weakness, increasing waxy pallor and shortness of breath. Physical examination showed marked anemia with a subicteric tint. The spleen was slightly enlarged. Ewald test meal showed complete achylia (poorly chymified contents, no Congo red, phenolphthalein 18). The blood (Table 4) showed all the typical changes of pernicious anemia. Wassermann reaction negative. The feces contained no blood or parasite eggs. The urine did not contain albumin, blood, pus or sugar. Under treatment the patient improved. On February 7, the patient had a chill followed by high fever of one day's duration. The urine now contained pus and numerous colon bacilli. The improvement continued, the type of anemia changed to the picture of simple anemia and the patient was discharged, March 23, 1920.

She very soon became worse and was sent to another hospital, where one of us had occasion to examine her May 1. The anemia was still of the simple anemia type and the patient recovered rapidly. On December 1, she was readmitted to our clinic with all the signs of severe typical pernicious anemia. She now did not respond to treatment and died on Jan 12, 1921. Necropsy showed extreme anemia, slight jaundice and red bone marrow, but no other changes.

## SUMMARY

1 Three cases in one family are reported, all of which showed gastric achylia, while two of them suffered from typical pernicious anemia and one from a pronounced microcytic anemia.

2 A case of typical pernicious anemia is reported in which the index during a remission and part of a relapse fell far below one, so that the picture in this and other respects resembled that of a simple anemia.

3 The behavior of the index in various stages of pernicious anemia is analyzed on the basis of a material of fifty-four cases.

# THE INCIDENCE OF SYPHILIS OF THE AORTA WITH INTERSTITIAL AND PARENCHYMATOUS NEUROSYPHILIS

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Our understanding of syphilis has undergone marked change of late years. Yet we still have more to learn than we already know and there is urgent need for new lines of investigation. The etiology of certain lesions that a few years ago were in dispute has been cleared up by the Wassermann test. Recent experimental animal researches and thousands of spinal fluid examinations have definitely established the fact that the invasion of the nervous system occurs in the early stages of the disease. Syphilologists are now quite generally agreed that we must consider different strains of the *Spinochaeta pallida* that have special predilection for special system, organs or tissues, just as we accept a bovine and human type of tubercle bacilli and numerous types of cocci and bacilli with special affinity for certain tissues. These facts explain many different phenomena observed in cerebrospinal and visceral syphilis.

The study of the frequency of neurosyphilis and cardiovascular syphilis dates back to about 1870. There was much difference of opinion among earlier workers. Some thought, for instance, that aortic disease was rare in tabes, while others spoke of its frequent occurrence. These early investigations of general paralytic and tabetic patients went far to establish the clinical entity, syphilitic aortitis. It was conceded that general paralysis and tabes were at least the result of syphilis before aortitis and aneurysm were considered as caused by syphilis. Too much reliance cannot be placed on earlier statistical studies of the frequency of the combined types of infection. Much confusion undoubtedly existed between arteriosclerosis and specific aortitis.

## REVIEW OF THE LITERATURE

Straub,<sup>1</sup> in 1899, found that 82 per cent of eighty-four general paralytic patients had aortitis. Lesser,<sup>2</sup> in 1905, reported nineteen

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1 Straub, quoted from Ophuls, W. Some Notes on Arteriosclerosis of the Aorta, *Am J M Sc* **131** 978, 1906.

2 Lesser. Zwei Fälle von Syphilitischen Exanthem, *Berl klin Wchnschr* **42** 991, 1905.

aneurysms in 100 tabetic patients, while Balacakis<sup>3</sup> only found three cases of aortitis in fifty-five tabetic patients. Friedman<sup>4</sup> has recently reviewed the earlier literature on this subject and reports various observers' statistics. This was the only paper of late years that we could find on the subject. Stevens<sup>5</sup> in a recent textbook states "Late syphilitic lesions of the aorta are common associations of tabes." Other authorities give lower percentages on the associated incidence of specific aortic and parenchymatous nervous lesions. Hubert,<sup>6</sup> in 220 cases of syphilitic aortitis, found that 25 per cent showed tabes. Guilly<sup>7</sup> reports that 20 per cent of 200 paralytic patients that came to necropsy showed late aortitis. Any study such as these has a personal equation in the diagnosis of syphilitic aortitis. The pathology considered syphilitic aortitis by one pathologist might not be so diagnosed by another. Warthin<sup>8</sup> states "The gross appearance of the aorta is no absolute criterion of aortic condition, when gross appearance of syphilitic aortitis is present the pathologic diagnosis can be made but with atherosclerosis no positive exclusion of syphilis can be made without the microscope." He<sup>9</sup> also says "My pathologic experience makes me believe the heart and aorta of every syphilitic patient are involved in the infection." In leveling statistical studies it seems that most observers have found late syphilitic aortitis in from 20 to 30 per cent of cases of tabes and general paralysis. We must assume that practically 100 per cent of syphilitic patients have focal nests of spirochetes in their aorta, since they can be found in all cases after diligent search.

While observations on the associated infection of the aorta in tabes and general paralysis are common, we are unable to find comparative studies of the frequency of syphilitic aortitis (especially aneurysms) with interstitial (endarteritic and meningeal) and parenchymatous (tabes and general paralysis) types of neurosyphilis. Neither did we find any large group of aneurysms with spinal fluid studies. This seemed important to us in view of the possibility of

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3 Balacakis, E. Des lésions aortiques chez les ataxiques, Paris theses, 64 59, 1883.

4 Friedman, E. D. The Associated Incidence of Syphilis of the Central Nervous System and Cardiovascular Syphilis, *Arch Neurol & Psychiat* 1 289 (March) 1919.

5 Stevens, A. A. The Practice of Medicine, Philadelphia, W. B. Saunders Co., 1922, p. 983.

6 Hubert, G. H. Zur Klinik und Behandlung der Aortensyphilis, *Arch f klin med* 28 317, 1918.

7 Guilly. Aorte et syphilis fréquence de la coexistence chez les syphilitiques des aortites avec le tabes et la paralysie générale, *Syphilis*, Paris, 3 258, 1905.

8 Warthin, A. S. The New Pathology of Syphilis, *Am J Syphilis* 2 425 (July) 1918.

9 Warthin, A. S. Spirochetes in Tissue of Cured Syphilis, *Am J M Sc* 152 520 (Oct) 1916.

determining whether there is more than one type of spirochetal infection, and whether advanced aortic lesions are more frequent in either variety of neurosyphilis. With this in mind we have undertaken the following study.

The cases of aortitis (aortic insufficiency and aneurysm) admitted to the men's medical department of the Philadelphia General Hospital from February to July, 1923, were examined. Thirty patients with syphilitic aortitis, showing clear cut physical signs, positive blood Wassermann tests or with a history of syphilis were collected. These cases of aortitis either showed the presence of an aneurysm or had an aortic insufficiency. Patients with systolic aortic murmurs with positive Wassermann tests were not included, as there might have been a question of the correct diagnosis. Furthermore, diagnoses were confirmed by roentgen-ray examinations and when possible by necropsy. Spinal fluid examinations were made on all these patients. Several hundred records of aneurysms were reviewed in an attempt to enlarge this group, but to our surprise we were able to find only very few cases of aneurysms where spinal fluid examinations were made. We might assume that in all these cases either there did not seem to the clinicians to be indication for the examination, or else the possibility of associated cerebrospinal infection was not looked for. In order to determine more accurately the associated incidence of aortic with interstitial and parenchymatous syphilis, 6,363 necropsy records from 1906 to 1923 from the Pathological Laboratory of the Philadelphia Hospital were reviewed. We collected from this number 110 general paralysis, 102 cerebrospinal syphilis and fifty cases of tabes in which descriptions of the aorta were given.

#### CLINICAL STUDY

In the thirty clinical cases, fourteen had demonstrable aneurysms, eleven were of the aortic arch, two of the abdominal aorta and one of the innominate artery (confirmed at necropsy). The other sixteen were cases of syphilitic aortitis with aortic regurgitation except one, which patient had angina pectoris. When roentgen-ray examinations were made they confirmed the clinical findings. In a few cases it was impossible to secure a roentgen-ray examination. Twenty-seven patients gave positive blood Wassermann tests of varying degrees. Of the three having negative blood reactions one patient showed advanced syphilitic aortitis at necropsy, one gave a chancre history and a plus Wassermann prior to admission and had received treatment and the other gave a positive spinal fluid reaction.

Spinal fluid examinations revealed the following. There were six definitely pathologic fluids, 20 per cent. Five gave positive Wassermann reactions, 16.6 per cent, four positive in all antigens and one in cholesterol alone. The other case had increased globulin, cell count



*Aneurysm and Syphilitic Aortitis Cases*

Case	Color	Diagnosis	Blood Wassermann	Spinal Fluid
1	B	Abdominal aneurysm	++++ cholesterol	Globulin not increased, no cells, Wassermann negative, 0011110000
2	W	Aneurysm of ascending arch of aorta, confirmed at necropsy	++++ all antigens	Brain showed early sclerosis, no findings of syphilis
3	W	Aneurysm of aortic arch, confirmed at necropsy	++++ all antigens	Trace of globulin, 6 cells per cmm, Wassermann negative, 1122200000
4	B	Aneurysm of innominate artery, confirmed at necropsy	Negative	Globulin not increased, 1 cell, Wassermann negative, 0000000000
5	B	Aneurysm of arch of aorta	++++ all antigens	Globulin not increased, no cells, Wassermann negative, 0000000000
6	W	Aneurysm of arch, ruptured left hemithorax	+++ cholesterol	Globulin not increased, no cells, Wassermann negative, 0000000000
7	W	Aneurysm of arch	++ cholesterol	Globulin not increased, 4 cells, Wassermann negative, 0000000000
8	W	Aneurysm of arch, cerebrospinal syphilis	++++ all antigens	Globulin, heavy trace, 50 cells, Wassermann positive, all antigens, 5555431110
9	W	Aneurysm of arch	++++ all antigens	Wassermann negative
10	B	Aneurysm of descending arch	Negative	Globulin not increased 3 cells, Wassermann, ++ cholesterol, 2200000000
11	W	Aneurysm of arch	++++ cholesterol	Globulin, no increase, cells none, Wassermann negative, 0000000000
12	W	Aneurysm of ascending arch	++++ cholesterol	Globulin no increase, no cells, Wassermann negative, 0000000000
13	W	Aneurysm, abdominal	++++ all antigens	Globulin no increase, cells none, Wassermann negative, 0000000000
14	W	Aneurysm of ascending arch	++++ cholesterol	Globulin, no increase, cells 3, Wassermann negative, 0000000000
15	B	Syphilitic aortitis, aortic insufficiency, left hemiplegia	++++ cholesterol	Wassermann ++, all antigens, 1124110000
16	W	Syphilitic aortitis, aortic insufficiency, cardiac psychosis	++++ cholesterol	Trace of globulin, no cells, Wassermann negative, 0000000000
17	B	Syphilitic aortitis, aortic insufficiency	++++ all antigens	No increase of globulin, 6 cells, Wassermann negative
18	B	Syphilitic aortitis, aortic insufficiency, general paralysis	++++ all antigens	Wassermann +++++, all antigens, 5554321000
19	W	Syphilitic aortitis, aortic insufficiency	++++ cholesterol	Globulin no increase, cells, no increase, Wassermann negative, 0000000000
20	W	Syphilitic aortitis, aortic insufficiency	++++ all antigens	Globulin, no increase, cells, none, Wassermann negative, 0000000000
21	W	Syphilitic aortitis, angina pectoris	+++ cholesterol	Globulin, no increase, cells none, Wassermann negative, 0000000000
22	B	Syphilitic aortitis, aortic insufficiency	Negative	Wassermann negative, 0000000000
23	B	Syphilitic aortitis, syphilitic myocarditis	+++ cholesterol	Globulin, no increase, 6 cells, Wassermann negative, 0000000000
24	B	Syphilitic aortitis, aortic insufficiency	++++ all antigens	Wassermann negative, 0000000000
25	W	Syphilitic aortitis, aortic insufficiency	++++ all antigens	Globulin, no increase, cells, none, Wassermann negative, 0001100000
26	B	Syphilitic aortic insufficiency, manic depressive psychosis	++++ all antigens	Wassermann negative
27	W	Syphilitic aortitis, aortic insufficiency	++++ all antigens	Globulin, no increase, cells, 10, Wassermann negative, 0000000000
28	W	Syphilitic aortitis, aortic insufficiency	++++ all antigens	Wassermann negative, 0000000000
29	W	Syphilitic aortitis, general paralysis, necropsy	++ Noguchi	Globulin increased, cells, 5, Wassermann +++++, 555555200
30	B	Syphilitic aortitis, aortic insufficiency	++++ cholesterol	Bloody fluid, ++ cholesterol

and a gold curve Three of these showed Lange gold curves which were in the general paralytic zone Two had strong syphilitic curves and one atypical Four of the positive cases showed clinical signs, two were diagnosed general paralysis, one cerebrospinal syphilis and one cerebral thrombosis None showed signs of tabes The two other positive cases had no clinical signs of nervous syphilis One extreme case of aortic regurgitation had an organic psychosis of cardiac origin with a negative spinal serologic reaction The vascular pathology in the six positive cases was three aneurysms of the aortic arch, and three syphilitic aortitis with aortic insufficiency The remaining twenty-four showed negative spinal fluids and had no clinical evidence of cerebrospinal syphilis Twelve of these patients were negroes and eighteen were whites Two of the positive fluids were in negroes and four were in whites

#### PATHOLOGIC STUDY

In the review of the necropsy records of the neurosyphilis cases, only those diagnosed syphilitic aortitis by the pathologist were accepted as absolute, unless from the gross description of hyaline plaques, puckering, scarring or dilatation of the aorta one could conclude the specimen to be specific aortitis Routine microscopic studies of the aorta have only been done in recent years in this hospital No intensive studies to demonstrate spirochetes in these cases have been made The following statistical report then should only be interpreted as covering advanced or late syphilitic aortitis

Interstitial neurosyphilis These were endarteritic cases of cerebral thromboses in young adults, chronic gummatous meningitis or meningo-myelitis cases In 102 cases there were thirty-eight, or 27 per cent, showing late syphilitic lesions of the aorta Nine of these (89 per cent) had large saccular aneurysms six were of the aortic arch, one abdominal aorta, one thoracic aorta and one vertebral artery There were thirty-nine negroes and sixty-three whites, thirteen of the negroes had syphilitic aortitis and three had aneurysms

Parenchymatous neurosyphilis Out of the 110 cases in which the lesions of the cortex were diagnosed as general paralysis, there were thirty aortas with advanced syphilitic aortitis, or 27 per cent Four of these, 36 per cent, had aneurysms three of the ascending aorta and one of the left ventricle There were twenty-eight negroes, four of these had associated syphilitic aortitis but no aneurysms

In fifty necropsies on tabetic patients (three cases classified as taboparesis were included) thirteen, or 26 per cent, were found to have old specific aortic lesions There was no true saccular aneurysm in the group Three were negroes, one of these had syphilitic aortitis

## COMMENT

In our clinical group of aortitis and aneurysms 20 per cent showed undoubted pathologic spinal fluids. This is in accordance with the figures given by Wile and Marshall<sup>10</sup> in 1,869 spinal fluid studies in all stages of the disease. They concluded that from 20 to 30 per cent of all syphilitic patients have pathologic spinal fluids, their standard for study was increased globulin, a cell count of over six, Wassermann tests and Lange gold curves. They state that from 15 to 30 per cent of syphilitic patients have also cerebrospinal syphilis. Since this occurs early in the infection, they assume it must be due to a specificity of the spirocheta. McDonald<sup>11</sup> examined forty unselected neurosyphilitic patients by roentgen ray, he found that eighteen, or 45 per cent, showed specific aortitis. We were unable to find this high a percentage by necropsy. We doubt whether the roentgen ray is a more reliable criterion for the diagnosis of this condition than the pathologist.

It is interesting that none of the clinical cases had signs of tabes, neither were there any aneurysms in the fifty necropsied tabes cases. Friedman<sup>4</sup> in his study brings out the fact that in tabes the aortic lesions may be mild. He says "One condition usually dominates the picture," and adds, "this may be due to variations in tissue or strains of spirochetes." Lucke and Rea<sup>12</sup> in a study of a large group of aneurysms illustrate the greater frequency of aneurysms in certain races, notably the higher incidence among negroes and the comparative rarity of tabes among them. They too suggest that certain spirochetal strains may have a selective affinity for the cardiovascular apparatus. Zimmermann,<sup>13</sup> in a comparative study of syphilis in whites and negroes, found that the negro developed endarteritic and meningeal forms of cerebrospinal syphilis associated with syphilitic aortitis but rarely had tabes and aortitis, while in white patients aortitis was more frequently associated with tabes and less frequently combined with the endarteritic type of cerebrospinal syphilis. The incidence of whites to negroes in our group of interstitial cases was approximately two whites to one negro, in the general paralysis three whites to one negro, and in tabes six to one. The ratio of whites to negroes admitted to the Philadelphia Hospital is about four to one. We are inclined to believe from our

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10 Wile, U J, and Marshall, C H. A Study of Spinal Fluid in One Thousand Eight Hundred and Sixty-Nine Cases of Syphilis in all Stages, *Arch Dermat & Syph* 3 272 (March) 1921.

11 McDonald, C A. The Heart and Arch by X-ray in Neurosyphilis, *J Nerv & Ment Dis* 57 509, 1923.

12 Lucke, Baldwin, and Rea, Marion H. Studies on Aneurysm, *J A M A* 77 935 (Sept 17) 1921.

13 Zimmermann, E L. A Comparative Study of Syphilis in Whites and in Negroes, *Arch Dermat & Syph* 4 75 (July) 1921.

studies that syphilitic aortitis and aneurysms are more frequently associated with neurosyphilis of the endarteritic and meningeal types regardless of race, but that general paralysis and more particularly tabes are less frequent in the negro

The necropsy studies were instructive in comparing the frequency of aortic lesions in the interstitial and parenchymatous types. Syphilitic aortitis and aneurysm were more frequent in the cerebrospinal vascular group. 38 per cent had advanced specific aortitis and 89 per cent had in addition saccular aneurysms. This is a 10 per cent higher incidence of late syphilitic aortitis than the much larger group of general paralysis and tabes. There were more than twice as many aneurysms in the 102 interstitial cases than in the combined parenchymatous group of 160 cases. This observation would seem to point to a specialized type of infection, a selective affinity for the cardiovascular system by one strain of spirochete and a highly neurotoxic virus in another strain. Experimental proof is abundant in the work of Noguchi, Levaditi and Marie, Nichols, Reasoner and others who have described different strains of spirochetes and shown these to have different cultural and morphologic characteristics. Furthermore, each strain produces entirely different initial, secondary and tertiary lesions. Levaditi and Marie<sup>14</sup> have inoculated rabbits with more than one strain of spirochetes, showing that inoculation with one strain does not protect against another. This observation may account for some of the reinfections seen in human beings. In this present year, Plaut and Muelzer<sup>15</sup> have reproduced in rabbits histologic changes similar to general paralysis in human beings, from two cases in which the spirochetes were isolated from general paralytic brains.

#### CONCLUSIONS

1. A clinical study of spinal fluids, obtained from thirty cases of syphilitic aortitis of which fourteen were aneurysms, showed that 20 per cent had associated cerebrospinal infection.

2. A comparative necropsy study of the frequency of associated late aortic syphilis with different varieties of neurosyphilis was done. In 102 cases of vascular neurosyphilis, 38 per cent had late syphilitic aortitis and 89 per cent had advanced to the stage of aneurysm. While in 110 general paralytic patients, 28 per cent had syphilitic aortitis with 34 per cent aneurysms and 26 per cent of fifty tabetic necropsies revealed syphilitic aortitis with no aneurysms.

<sup>14</sup> Levaditi, C, and Marie, A. Plurality of Spirochetes in Syphilis, *Présse Med* 28 646 (Sept 15) 1920, abstract, *J A M A* 75 1457 (Nov 20) 1920.

<sup>15</sup> Plaut and Muelzer. Action of Different Strains of Spirochetes, *Munchen med Wchnschr* 69 1779 (Dec 29) 1922, abstract, *J A M A* 80 735 (March 10) 1923.

3 Advanced syphilis of the aorta and resulting aneurysms are more frequently associated with the endarteritic and meningeal (interstitial) form of cerebrospinal syphilis than with the parenchymatous (tabetic and general paralytic) variety. In the early stage of spirochetemia there is invasion of every aorta. In certain persons there occurs extensive vascular disease, probably the result of vasotropism of the *Spirochaeta pallida*. In others, the aortic lesions are mild, and the strain of spirochete has higher invasive qualities and attacks nervous tissue with resulting neuronie degeneration by the neurotropic strain.

# THE RELATION OF THE SUPRARENALS TO CHOLESTEROL METABOLISM<sup>1</sup>

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It has been shown by histologic and chemical studies that the cortex of the suprarenal is particularly rich in lipoids, especially cholesterol and its esters. It has also been demonstrated that these cortical cells hypertrophy during the hypercholesterinemia of pregnancy<sup>1</sup> and that pregnant animals survive fatal extirpation of the suprarenals much longer than nonpregnant animals<sup>2</sup>. In addition to this, several workers have noted in the experimental hypercholesterinemia due to high cholesterol feeding, and also in the pathologic and physiologic hypercholesterinemias, that there has been a constant increase in the lipid content of the cortex of the suprarenals. Wacker and Hueck<sup>3</sup> have demonstrated that animals that had been fed cholesterol preoperatively definitely lived longer after bilateral suprarenalectomy. These observations, together with the work of Chauffard and his school in France, and the German workers (Aschoff, Rothschild, Landau and McNee) strongly suggest that some definite relationship exists between the suprarenal glands and the cholesterol metabolism of the body.

Just what this relationship may be has not been determined, but several different views have been advanced. Aschoff's school considers the changes in the suprarenal to be secondary to the hypercholesterinemia and that the suprarenal merely acts as a "depot organ" for the cholesterol. Their opinions are based, to some extent, on the experimental work of Rothschild<sup>4</sup> and Landau and McNee<sup>5</sup>. The former performed unilateral and bilateral suprarenalectomies on rabbits and

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<sup>1</sup> From the Section of Surgery, Yale University School of Medicine

1 Sternberg, H. Die Nebenniere bei physiologischer (Schwangerschaft—) und artifizieller Hypercholesterinämie, Beitr z path Anat u z allg Path 60:91-123, 1915

2 Stewart, H. A. On Certain Relations Between Lipoid Substances and the Adrenals, Seventeenth International Congress of Medicine, London, 1913, Section III, Part II, p 173-181

3 Wacker, L., and Hueck, W. Cited by Rothschild (4)

4 Rothschild, M. A. Zur Physiologie des Cholesterinstoffwechsels III Die Beziehungen der Nebenniere zum Cholesterinstoffwechsel Beitr z path Anat u z allg Path 60:39-65, 1915

5 Landau, M., and McNee, J. W. Zur Physiologie des Cholesterinstoffwechsels Beitr z path Anat u z allg Path 58:667-699, 1914

studied the changes in the cholesterol content of the blood, the bile and the suprarenals. After the removal of one suprarenal, he noted a sharp rise in blood cholesterol during the first twenty-four hours after operation, which was followed by a fall and then a secondary gradual rise which reached its highest point at about the twelfth day. In the few animals which were studied for longer periods, this high point was followed by a rather sudden fall in the cholesterol content of the blood to below normal and then there was a gradual rise so that a practically normal figure was reached on about the twenty-first day postoperatively. In those animals in which both suprarenals were removed, Rothschild reported a more progressive hypercholesterinemia continuing until the animal died which usually occurred within twenty-four hours. Landau and McNee<sup>5</sup> studied the free and cholesterol ester content of the suprarenals in rabbits which were given olive oil and cholesterol in olive oil by mouth and intraperitoneally and found a definite increase, due practically entirely to cholesterol esters.

The French School, headed by Chauffard, have done a large amount of work on cholesterol. They have maintained in many of their papers<sup>6</sup> that the suprarenals are capable of synthesizing this substance, and that the blood changes are secondary to the increased cholesterol production of the suprarenal cortex. This theory is based to some extent on the experimental work of Grigaut,<sup>6</sup> who followed the changes in the cholesterol content in the blood of dogs after unilateral and bilateral suprarenalectomies. He found that, following the removal of one suprarenal, there was a short period during which no change occurred in the blood cholesterol. After this latent period, a hypercholesterinemia developed which reached its maximum on the twelfth day and returned to normal on the twenty-first day. After bilateral suprarenalectomy no change was found in the cholesterol content of the blood. Grigaut interpreted these findings in the following way. After the unilateral suprarenalectomies the latent period, during which there was no change in the blood cholesterol, was due to the period of time necessary for the remaining suprarenal to hypertrophy and hyperfunction. The absence of an increased cholesterol content of the blood following bilateral suprarenalectomy was due to the removal of the organ which secretes the cholesterol.

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<sup>6</sup> Grigaut, A. Le metabolisme de la cholestérine, Part III. Le cycle de la cholestérinémie, These de Paris, Paris, 1913. Grigaut, A., and L'Huillier, A. Hypercholesterinémie d'origine alimentaire chez le chien, *Compt rend Soc de Biol* **73** 304-307, 1912. Chauffard, A., La Roche, G., and Grigaut, A. La cholestérinémie a l'état normal et pathologique *Ann de med* **8** 69-91 (Aug) 1920, Le cycle de la cholestérine dans l'organisme *Ann de med* **8** 149-172, 1920, Les depots locaux de cholestérine, *Ann de med* **8** 321-334 (Nov) 1920. La Roche, G. Suprarenals and Cholesterol, *Rev franç d'endocrin*, Paris, **1** 185, 1923.

In a more recent work Baumann and Holly <sup>7</sup> have studied in rabbits the effects of suprarenalectomy on the cholesterol and lipid phosphorus content of the blood. They observed no increase in the blood cholesterol after unilateral suprarenalectomy, in fact, six out of ten of the uncomplicated experiments showed a decrease amounting to about 15 per cent. In the animals that survived double suprarenalectomy for five weeks or more, there were no changes in the blood cholesterol. However, there was a terminal rise which the authors considered only as one of the terminal effects. They divide their series of animals into two groups: "Class A, those dying within four or five weeks, and Class B, those living for four or five months or indefinitely." Six rabbits fell into each group. It seems quite evident that if the animals survived removal of the second suprarenal gland for such long periods of time, a severe degree of suprarenal insufficiency could not have been produced. All their bilateral suprarenalectomies, except one, were done in two stages, the second suprarenal being removed from two to seven weeks after the first. Rabbits fairly frequently have accessory suprarenal tissue, and the period between the first and second suprarenalectomy would give sufficient time for this tissue to hypertrophy enough to be able to take over the burden after removal of the second suprarenal. Elliott <sup>8</sup> found this to occur quite frequently in cats. It is interesting to note that the only rabbit in which they removed both suprarenals at once (Rabbit 304), showed a definite increase in the cholesterol content of the blood during the first week after operation and that this increase steadily became more marked until the death of the animal.

While both Rothschild and Grigaut observed a hypercholesterinemia following the unilateral suprarenalectomies, their results in the cases of bilateral suprarenalectomies are quite different. Various factors which might have caused the differences in the findings of all these investigators are as follows:

1 *Diet*—None of the previous workers seemed to have sufficiently controlled the diet of the animals before or after operation. The animals evidently were permitted to eat as much as they wanted of the usual laboratory diet, without any apparent attempt being made to establish a uniform and constant intake. Baumann and Holly state that their rabbits were kept on a uniform diet of alfalfa, oats and carrots, but the

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7 Baumann, E. J., and Holly, O. M. The Relation of Lipoids to Suprarenal Physiology. I. The Cholesterol and Lipoid Phosphorus Contents of the Blood of Rabbits Before and After Suprarenalectomy, *J. Biol. Chem.* **55** 457-475 (March) 1923.

8 Elliott, T. R. Some Results of Excision of the Adrenal Glands, *J. Physiol.* **49** 38-53, 1915.



amount of diet apparently was not calculated in calories per kilogram of body weight

That the cholesterol in the blood is influenced by the quantity of this substance in the food has been quite definitely established<sup>9</sup> Furthermore, Luden<sup>10</sup> has shown that the various foodstuffs vary greatly in their cholesterol content Egg yolk contains 888 mg of cholesterol per hundred grams, butter 298, beef, 53, cream, 61 mg per hundred cubic centimeters, milk, 28, and oatmeal 0 This author<sup>11</sup> has also studied the effects of various types of diets on the blood cholesterol, and found that on a simple diet, consisting mainly of milk, bread, lettuce and jam, there was a definite decrease in total cholesterol in three days, on an exclusive meat diet (from 1¼ to 1½ pounds [about 7 to 9 gm] per day) a very marked increase resulted (about 100 per cent in seven days), while on a vegetable diet, the blood cholesterol again definitely dropped Rothschild<sup>12</sup> has shown in experiments on rabbits that starvation causes an increase in the cholesterol content of the blood, liver, bile and suprarenals Gardner and Lander<sup>9</sup> also describe as a rise in the blood cholesterol during inanition Experiments such as these show the necessity, before and after operation, of a uniform and adequate diet which has been calculated in calories per kilogram of body weight After operation, another difficulty is encountered in the varying appetites of the animals Some of them refuse all food, others are not affected at all, and still others may partake of small amounts of food

2 *Experimental Animals*—The type of animal used may very easily be conceived to make a difference in the results obtained Grigaut used dogs, while Rothschild and Baumann and Holly used rabbits The latter, and other herbivora, evidently have a rather sluggish cholesterol metabolism Relatively small amounts of cholesterol are found in the bile, so that a considerable increase in the blood cholesterol is necessary

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9 Gardner, J A, and Lander, P E On the Cholesterol Content of the Tissues of Cats under Various Dietetic Conditions and During Inanition, *Biochem J* **7** 576-587, 1913 Sternberg (Footnote 1) Grigaut, Grigaut and Hulier, Chauffard, La Roche and Grigaut, La Roche (Footnote 6) Luden (Footnotes 10 and 11)

10 Luden, G Changes in the Cholesterol Content of the Blood of Goats, Following Cholesterol Feeding Alone, Roentgen Treatment Alone, and Cholesterol Feeding Combined with Roentgen Treatment and Subsequent Castration, *Jour Biol Chem* **27** 273-297 (Oct) 1916

11 Luden, G Studies on Cholesterol IV Experiments Concerning the Relation of the Diet, the Blood Cholesterol, and the "Lymphoid Defense," *J Lab & Clin Med* **3** 141-172 (Dec) 1917, Studies on Cholesterol VI The Value of Blood Cholesterol Determinations and Their Place in Cancer Research, *J Lab & Clin Med* **4** 719-735 (Sept) 1919

12 Rothschild, M A Zur Physiologie des Cholesterinstoffwechsels V Der Cholesteringehalt des Blutes und einiger Organe im Hungerzustand, *Beitr z path Anat u z allg Path* **60** 227-231 1915

before there is any increased output in the bile. For this reason the blood of a rabbit will show much greater variations in the cholesterol content than that of a dog, in which animal the cholesterol metabolism is more active. As a result, any increase in the cholesterol in the blood readily finds its way out through the bile. In addition, rabbits much more frequently have accessory suprarenal tissue.

3 *Blood Volume and Concentration*.—The failure of all the previous investigators to determine the changes in the blood concentration, together with the cholesterol changes makes it difficult properly to evaluate their work. Donath<sup>13</sup> states that in cats, the blood solids increased from an average of 19.6 to 24.5 per cent following suprarenalectomy. A change in blood concentration necessarily carries with it a corresponding change in the various constituents of the blood.

In the experiments which follow, an attempt has been made to determine the effect of unilateral and bilateral suprarenalectomies on the blood cholesterol of dogs. The animals have been kept on carefully calculated constant diets and the changes in the blood concentration and other constituents of the blood have been studied, together with the changes in cholesterol.

#### METHODS

Healthy young dogs were used in these experiments, and so far as possible, males were selected in order to rule out the possible influences that pregnancy might have on the cholesterol metabolism. Two different series of animals were studied. In Series A,<sup>14</sup> the blood cholesterol, blood sugar, nonprotein nitrogen, blood solids and hemoglobin were studied, while in Series B, the free cholesterol, cholesterol ester, and total cholesterol contents of the blood were determined in addition to the blood urea and blood solids.

*Diet*.—The dogs were fed daily until they were operated on. Following the unilateral suprarenalectomies, no food was given for twenty-four hours but water was given freely. Following the bilateral suprarenalectomies, or the removal of the second suprarenal, no further food was given but here again the animals were allowed to drink. In this way uniform dietary conditions were obtained with all the animals throughout the experiments.

In Series A, the diet was an adequate one for dogs under usual laboratory conditions. It consisted of 21.5 gm of lean meat, 5.0 gm of cracker meal and 3.0 gm of lard per kilogram of body weight daily.

13 Donath, J. Ueber den Einfluss der Nebennierenextirpation auf die Blutkonzentration bei Katzen, *Arch f exper Path u Pharmacol* **77**:1-15, 1914.

14 The dogs in Series A are designated by a letter (Dog A, Dog B, Dog C, etc), whereas those in Series B are numbered (Dog 13, Dog 16, etc).

The dogs in Series B received the diet which has recently been described by Cowgill<sup>15</sup> The kilogram unit daily of this diet is as follows

TABLE 1—*Kilogram Unit Daily of Diet*

	Amount Grams	Calories	Percentage
Casein, 81.9 % Pure 12.7 % Nitrogen	63	208	37.6
Sucrose	584	234	34.9
Lard	283	25.5	17.0
Butter Fat	117	10.5	7.0
Bone Ash	0.40		2.3
Salt Mixture	0.20		1.2
Total	1674	802	100.0

The salt mixture used was the one described by Karr<sup>16</sup>

TABLE 2—*Salt Mixture*

	Grams
Sodium Chlorid	10
Calcium Lactate	4
Magnesium Citrate	4
Ferric Citrate	1
Compound Solution of Iodin	a few drops

Vitamin B was given with the diet in the form of yeast vitamin powder (Harris), 60 mg per kilogram of body weight daily

*Cholesterol Determinations*—The blood cholesterol determinations were made by the colorimetric method of Bloor<sup>17</sup> and Bloor and Knudson<sup>18</sup>

In the determinations made on the dogs in Series B, the method described by Bloor and Knudson<sup>18</sup> was followed exactly Three cubic centimeters of blood were slowly dropped from a previously calibrated pipet into about 75 cc of a mixture of redistilled alcohol and ether (3 parts of alcohol to 1 part of ether) in a 100 cc volumetric flask The flask was shaken constantly during the transfer The contents of the flask were then raised to boiling point on a water bath, with constant shaking to avoid superheating, cooled to room tempera-

15 Cowgill, G. R. An Improved Procedure for Metabolism Experiments J Biol Chem 56 725-737 (July) 1923

16 Karr, W. G. Some Effects of Water-Soluble Vitamin on Nutrition, J Biol Chem 44 255-276 (Nov) 1920

17 Bloor, W. R. The Determination of Cholesterol in the Blood, J Biol Chem 24 227-231 (March) 1916

18 Bloor, W. R., and Knudson, A. Separate Determination of Cholesterol and Cholesterol Esters in Small Amounts of Blood, J Biol Chem 27 107-112 (Oct) 1916

ture, filled to the mark with more alcohol-ether mixture, and then filtered. Ten cubic centimeters of this filtrate were measured into a small flat-bottomed beaker and evaporated just to dryness on an electric stove. The cholesterol was extracted from the dry residue by "boiling out" three or four times with successive small amounts (about 4 c c) of chloroform, and decanted into a 10 c c glass stoppered graduated cylinder. These combined extracts after cooling were then made up to 5 c c.

From 20 to 30 c c of the filtered alcohol-ether extract was measured into a 50 c c Erlenmeyer flask and 1 c c of a 1 per cent alcoholic solution of digitonin added to this. The whole mixture was then evaporated just to dryness. (The digitonin combines with the free cholesterol to form digitonin-cholesterid but does not affect the cholesterol esters.) The dried residue in the flask was extracted by boiling with successive small amounts of petroleum-benzin (boiling below 60 C) and this extract filtered through a plug of fat-free cotton in the stem of a small funnel. (The petroleum-benzin dissolves the cholesterol-esters but not the precipitated digitonin-cholesterid.) The combined extracts were then evaporated just to dryness and the cholesterol esters taken up by boiling with successive small amounts of chloroform and decanted into a 10 c c glass stoppered graduated cylinder. These combined extracts were made up to 5 c c after cooling.

Five cubic centimeters of a standard solution of pure cholesterol (Merck) in chloroform (each cubic centimeter contains 0.1 mg of cholesterol) was measured into a similar 10 c c cylinder.

To each of these solutions were added 2 c c of acetic anhydrid and 0.1 c c of concentrated sulphuric acid. The solutions were mixed by inverting the cylinders several times and then allowed to stand for fifteen minutes at a temperature of from 20 to 22 C, and exposed to the same light as the readings were to be made by later.<sup>19</sup> After the color had developed, the solutions were read in a Duboscq colorimeter with the standard set at 15 mm. All determinations were made in duplicate.

In Series A (except in Dog G), the same method was used for determining the total cholesterol content of the blood,<sup>17</sup> except that instead of using a solution of pure cholesterol in chloroform as a standard, the animal's own blood was used, putting it through the same process as the unknown sample and considering its value as 100 per cent. This standard was used in an attempt to overcome the brownish tinge which occasionally occurs in the unknown sample and makes the colorimetric reading difficult and at times impossible. When this

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<sup>19</sup> Bloor, W. R., Pelkan, K. F., and Allen, D. M. Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, *J. Biol. Chem.* **52** 191-205 (May) 1922.

"blood standard" is used, the same impurities are present in both the standard and the unknown, and thus the readings are made more easily. In this way satisfactorily comparable results were obtained, although the readings were not in terms of milligrams per hundred cubic centimeters of blood. In Dog G, however, the usual standard was used and the figures here do represent milligrams per hundred cubic centimeters.

*Nonprotein Nitrogen, Blood Urea and Blood Sugar* — These determinations were made after the method of Folin and Wu<sup>20</sup>

The hemoglobin determinations were made by the Cohen and Smith method<sup>21</sup>

*Blood Solids* — Approximately from 0.5 to 1.0 gm of blood was drawn into weighed aluminum dishes, which were supplied with tightly fitting covers. After a second weighing the covers were removed and the blood dried in an oven at a temperature of 105°C for from twelve to eighteen hours, cooled in a desiccator for one-half hour, and weighed again. The percentage of total blood solids was then calculated from the weights of the whole and dried blood.

*Surgical* — All operations were performed with the usual aseptic technic. Ether anesthesia, preceded by morphin, was used. The supra-renalectomies were done through lumbar incisions.

The blood specimens were obtained from the jugular vein. The animals were fed daily at about 2 p.m. and the bleedings were made just before feeding.

#### PRESENTATION OF DATA

*Series A* — In this series, nine male dogs were used. Bilateral supra-renalectomies were done in one stage in four of them (Dogs A, B, C and D) and the total blood cholesterol, blood sugar, nonprotein nitrogen, blood solids, and hemoglobin were studied before and after operation. Three of these dogs showed very definite increases in the blood cholesterol after the operation, but the fourth one (Dog D) showed a slight drop. The necessity of studying the blood concentration by means of either the blood solids or hemoglobin is indicated in this dog. The preoperative average here for cholesterol was 104 per cent and for hemoglobin 98 per cent. Postoperatively, the cholesterol reading was 124 per cent, an apparent increase of 20 per cent, but as the hemoglobin reading was 126 per cent, it will readily be seen that this increase was due to the concentration of the blood. The blood sugar showed a drop in

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<sup>20</sup> Folin, O., and Wu, H. A System of Blood Analysis, *J. Biol. Chem.* **38** 81-110 (May) 1919, A Simplified and Improved Method for Determination of Sugar, *J. Biol. Chem.* **41** 367-374 (March) 1920.

<sup>21</sup> Cohen, B., and Smith, A. H. The Colorimetric Determination of Hemoglobin, *J. Biol. Chem.* **39** 489-496 (Oct.) 1919.

three of the four dogs and a negligible rise in one. However, it should be remembered that none of these dogs were fed after they were operated on. The nonprotein nitrogen showed a steady increase, which was very marked. An increased concentration of the blood was present in all (Protocols 1, 2, 3 and 4)

### PROTOCOL 1—Dog A, Male

Day	Actual Readings					Change from Preoperative Average Calculated in Relation to Blood Solids		
	Choles-terol	Mg Blood Sugar, per Cent	Mg Non-protein Nitrogen per 100 C c Blood	Blood Solids, per Cent	Hemo-globin, per Cent	Choles-terol	Mg Blood Sugar, per Cent	Mg Non-protein Nitrogen per 100 C c Blood
First	81	96	23	21 0	105			
Second	81	103	22	20 0	94			
Third	81	103	29	19 9	94			
Preoperative average	81	101	25	20 3	98			
Third, a m ,operation bilateral suprarenalectomy								
Third, p m	95	112	22	20 7	94	12	9	—3
Fourth	141	100	37	20 7	94	58	—3	12
Fifth	97	94	48	22 4	103	8	—18	20
Sixth	98		86	21 4	80	13		60

Died sixty two hours after operation Postmortem examination negative

### PROTOCOL 2—Dog B, Male

Day	Actual Readings					Change from Preoperative Average Calculated in Relation to Blood Solids		
	Choles- terol	Mg Blood Sugar, per Cent	Mg Non- protein Nitrogen per 100 C c Blood	Blood Solids, per Cent	Hemo- globin, per Cent	Choles- terol	Mg Blood Sugar, per Cent	Mg Non protein per 100 C c Blood
First	110	105	31	18.3	81			
Second	105	104	32	19.0	81			
Preoperative average	108	105	32	18.7	81			
Second, operation bilateral suprarenalectomy								
Third	139		39	19.3	91	28		6
Fourth	140	98	49	19.7	101	26	-13	15

Died forty hours after operation Postmortem examination negative

### PROTOCOL 3—Dog C, Male

Day	Actual Readings					Change from Preoperative Average Calculated in Relation to Blood Solids		
	Choles-terol	Mg Blood Sugar, per Cent	Mg Non-protein Nitrogen per 100 C c Blood	Blood Solids, per Cent	Hemo- globin, per Cent	Choles-terol	Mg Blood Sugar, per Cent	Mg Non-protein Nitrogen per 100 C c Blood
First	98	98	55	22.6	98			
Second	106	105	64	21.6	102			
Preoperative average	102	102	59	22.1	100			
Second, operation bilateral suprarenalectomy								
Thrd	141	114	84	23.5	121	32	5	21

Died twenty five hours after operation Postmortem examination negative

## PROTOCOL 4—Dog D, Male

Day	Actual Readings				Change from Preoperative Average Calculated in Relation to the Hemoglobin		
	Choles- terol	Mg Blood Sugar, per Cent	Mg Non- protein Nitrogen per 100 C c Blood	Hemo- globin, per Cent	Choles- terol	Mg Blood Sugar, per Cent	Mg Non- protein Nitrogen per 100 C c Blood
First	113			94			
Second	94	152	40	102			
Preoperative average	104	152	40	98			
Second, operation bilateral suprarenalectomy							
Third	124	117	153	126	-7	-77	102

Died twenty hours after operation Postmortem examination negative

The average duration of life following the bilateral suprarenalectomies of this group was thirty-seven hours, the longest duration being sixty-two hours, and the shortest twenty hours

In Dog E, a unilateral suprarenalectomy was done at one operation and the remaining suprarenal removed one week later. The first day after the unilateral suprarenalectomy there was a very marked increase in the blood cholesterol, followed on the next day by a decided drop, but the figures still remained well above normal. The blood sugar and nonprotein nitrogen both showed somewhat of an elevation above the preoperative average. After the removal of the remaining suprarenal, there was a further increase in the blood cholesterol on the first day after the operation, but this was followed by a steady decline to almost normal shortly before death. The blood sugar steadily diminished, but the nonprotein nitrogen steadily increased after the second operation. An increase in the blood concentration was indicated by the definite rise in the percentages of the blood solids and hemoglobin. This animal died sixty hours after the second operation (Protocol 5)

## PROTOCOL 5—Dog E, Male

Day	Actual Readings					Change from Preoperative Average Calculated in Relation to Blood Solids		
	Choles- terol	Mg Blood Sugar, per Cent	Mg Non- protein Nitrogen per 100 C c Blood	Blood Solids, per Cent	Hemo- globin, per Cent	Choles- terol	Mg Blood Sugar, per Cent	Mg Non- protein Nitrogen per 100 C c Blood
First	91	108		22.6	120			
Second	111	93	42	22.4	116			
Third	115	106	43	22.2	112			
Preoperative average	106	104	43	22.4	116			
Third, operation unilateral suprarenalectomy								
Fourth	176	110	46	20.9	100	77	13	6
Fifth	128	104	47	21.4	89	27	5	6
Ninth	130	103	48	20.5	95	33	13	9
Tenth	137	108	52	20.5	95	40	13	13
Average increase in one week following unilateral suprarenalectomy,						44	11	8
Tenth operation remaining suprarenal removed								
Eleventh	156	106	48	21.7	114	53	5	6
Twelfth	143	106	65	24.6	112	32	-8	18
Thirteenth	130	100	78	26.2	120	10	-20	26

Died sixty hours after operation Postmortem examination negative

In Dog G, the right suprarenal was removed at one operation and then half of the left was removed eleven days later. Daily bleedings were made and the total blood cholesterol, blood solids and hemoglobin followed. Twenty-four hours after the first operation there was a slight rise in the blood cholesterol followed by a fall to approximately normal, which lasted for forty-eight hours, and then a marked secondary rise. A week after the second operation still higher figures were obtained. During the first forty-eight hours after operation there was an increase in the blood concentration but following this there was a gradual drop, possibly due to the frequently repeated bleedings (Protocol 6)

PROTOCOL 6—Dog G, Male

Day	Actual Readings			Change from Preoperative Average Calculated in Relation to Blood Solids, Mg Cholesterol per 100 C e Blood
	Mg Cholesterol per 100 C e Blood	Blood Solids, per Cent	Hemoglobin, per Cent	
First	162	21.4	137	
Fourth	150	19.6	121	
Sixth	150	19.5	103	
Seventh	164	20.4	132	
Ninth	166	20.2	135	
Thirteenth	195	22.6	134	
Preoperative average	165	20.6	128	
Thirteenth, operation right suprarenalectomy				
Fourteenth	183	21.8	124	13
Fifteenth	174	23.0	141	-10
Sixteenth	163	19.7	121	0
Seventeenth	240	20.3	128	78
Nineteenth	201	19.0	128	49
Twentieth	192	20.4	115	28
Twenty first	199	20.6	120	34
Twenty-second	207	18.5	101	59
Twenty-fourth	234	18.2	101	88
Average increase in 11 days following unilateral suprarenalectomy				38
Twenty-fourth, operation half of left suprarenal removed				
Twenty fifth	194	19.0	110	42
Twenty sixth	230	19.7	99	72
Twenty-eighth	226	18.8	104	75
Thirty first	222	17.5	100	82
Thirty-third	244	17.8	109	101
Thirty fifth	256	17.5	100	116

Animal sacrificed sixteen months later, was in fine condition

Dog F had the entire right suprarenal and half of the left suprarenal removed at one operation and the total blood cholesterol, blood sugar, nonprotein nitrogen, blood solids and hemoglobin studied for six days after operation. In this animal there was a definite increase in the cholesterol for the entire period that it was followed. There was no definite change noted in the blood sugar nor the nonprotein nitrogen. The blood solids showed very little variation, although there was a fairly marked drop in the hemoglobin by the eighth day (Protocol 7)

In order to rule out the possible influence of an anesthetic or an operative procedure on the blood cholesterol, several dogs were run through as control experiments. In addition, since Gardner and Lander<sup>9</sup> and Rothschild<sup>12</sup> have shown that starvation will increase the blood



## PROTOCOL 7—Dog F, Male

Day	Actual Readings					Change from Preoperative Average Calculated in Relation to Blood Solids		
	Choles- terol	Mg Blood Sugar, per Cent	Mg Non- protein Nitrogen per 100 C c Blood	Blood Solids, per Cent	Hemo- globin, per Cent	Choles- terol	Mg Blood Sugar, per Cent	Mg Non- protein Nitrogen per 100 C c Blood
First	89	109	50	22.8	112			
Second	87			22.3	111			
Preoperative average	88	109	50	22.6	112			
Second operation removal of one and one-half suprarenals								
Third, a m	117	110	57	22.1	111	31	3	8
Third, p m	123	105	69	22.6	117	35	—4	19
Fourth	126	106	48	22.0	90	41	0	—1
Seventh	123	102	50	22.0	90	38	—4	1
Eighth	140	112	50	22.0	88	55	6	1

Animal in excellent condition at end of experiment

cholesterol, it was also necessary to determine whether short periods of starvation, such as were present in our dogs after bilateral suprarenalectomy, would influence it. Accordingly, after having been on the standard diet for three days, these dogs were operated on under ether anesthesia preceded by morphin and an exploratory laparotomy done, during which the intestines, suprarenals and other organs were manipulated. Following the operation the animals were starved for four days. In none of these dogs was there any definite change noted after the operation in the cholesterol content of the blood or the nonprotein nitrogen. There was, however, a slight drop in the blood sugar. The protocol of Dog M will serve as one typical of these control animals (Protocol 8).

## PROTOCOL 8—Control Experiment \*

Day	Actual Readings					Change from Preoperative Average Calculated in Relation to Blood Solids		
	Choles- terol	Mg Blood Sugar, per Cent	Mg Non- protein Nitrogen per 100 C c Blood	Blood Solids, per Cent	Hemo- globin, per Cent	Choles- terol	Mg Blood Sugar, per Cent	Mg Non- protein Nitrogen per 100 C c Blood
First	113	103	34	17.6	83			
Operation exploratory laparotomy								
Second	100	101	33	16.6	81	—7	—1	1
Third	110	94		16.7	70	3	—8	—
Fourth	113	91	40	17.1	78	3	—14	7
Fifth	115	105	28	17.8	115	1	—4	—6

\* Dog M—Young healthy male dog. Weighed 9 kg. Received standard diet for 3 days and then operated on. Ether anesthesia. Exploratory laparotomy performed with manipulation of the intestines, suprarenals, etc. Duration of operation, 1 hour.

In one of the dogs of this series (Dog N) an artificial hypercholesterinemia was produced by feeding the animal 1 gm. of cholesterol and giving subcutaneous injections of 10 gm. of hydrous wool fat daily for eleven days before performing a bilateral suprarenalectomy. In

this dog the blood cholesterol did not rise above the preoperative average until the second day after the operation. It remained up on the two following days but on the last day of life it dropped below the preoperative average. The blood sugar showed practically no change until the last day. The nonprotein nitrogen steadily increased until it reached an unusually high figure. The duration of life following a bilateral suprarenalectomy was apparently definitely increased in this case, as the dog lived for 124 hours after the operation, twice as long as the longest period obtained in the dog in which no preoperative hypercholesterinemia was produced. At necropsy no accessory suprarenal tissue was found (Protocol 9).

PROTOCOL 9—Dog N, Healthy Male Dog<sup>1</sup>

Day	Actual Readings					Change from Preoperative Average Calculated in Relation to Blood Solids		
	Cholesterol	Mg Blood Sugar, per Cent	Mg Non-protein Nitrogen per 100 C c Blood	Blood Solids, per Cent	Hemoglobin, per Cent	Cholesterol	Mg Blood Sugar, per Cent	Mg Non-protein Nitrogen per 100 C c Blood
First	118	106	34	21.6	84			
Tenth	150	98		21.1	97			
Eleventh	170	91		21.4	93			
Preoperative average	146	98	34	21.4	91			
Eleventh, operation	bilateral suprarenalectomy							
Twelfth	138	98	52	21.9	91	-11	-2	17
Thirteenth	180	92		21.7	99	32	-7	
Fourteenth	180	98	100	?	101	?	?	?
Fifteenth	180	97		21.8	101	31	-8	
Sixteenth	150	95	264	24.3	110	-16	-16	125

Died 124 hours after operation. Necropsy revealed no other possible cause of death. No accessory suprarenal tissue found.

<sup>1</sup> Dog N—Healthy male dog. Weighed 12 kg. Received 1 gm of cholesterol by mouth and 10 gm of hydrous wool fat subcutaneously each day during the experiment. Before operation the dog was given the standard diet, after operation, just the cholesterol and hydrous wool fat.

**Series B**—In this series eight dogs were used. Cowgill's diet was used instead of the one consisting of meat, cracker meal and lard. In addition to studying the total cholesterol content of the blood, the ratio between the free cholesterol and cholesterol ester was determined. The blood urea and blood solids were also followed.

In four of the dogs bilateral suprarenalectomies were done at one operation (Dogs 13, 16, 45 and 46). Two of these dogs showed definite increases in the blood cholesterol after the operation (Dogs 13 and 45). Dog 16 showed a transient increase of about 8 per cent and in Dog 46 there was an increase of only 10 per cent, not enough in either case to be considered a definite rise. In Dog 45 the increase was caused entirely by the free cholesterol but in the other dogs it was fairly evenly divided between free cholesterol and the cholesterol esters. The blood urea became elevated in all four animals. The blood solids exhibited no constant change. The average duration of life after operation in this

group was twenty-five hours, the shortest being sixteen hours and the longest thirty-six. It is interesting to note that the dog which lived the longest showed an early pregnancy at necropsy (Protocols 10, 11, 12 and 13)

PROTOCOL 10—Dog 13, Male, weighed 111 kg

Date	Actual Readings					Change from Preoperative Average Calculated in Relation to Blood Solids				Remarks
	Mg Cholesterol per 100 C e Blood			Blood Solids, per Blood Cent	Urea	Mg Cholesterol per 100 C e Blood			Blood Urea	
	Free	Ester	Total			Free	Ester	Total		
11/ 6/23										Dog put on constant diet
11/ 9/23	151	89	240	21.1	26					Active, not eating well, mild conjunctivitis
11/11/23	145	80	225	19.9	22					Active, appetite good, eyes all right, weight, 10.9 kg
11/12/23	131	92	223	19.6						Dog in very good condition, appetite excellent
Preoperative average 11/12/23	142	87	229	20.2	24					Operation bilateral suprarenalectomy at 3.30 p.m.
11/13/23 30 hours postoperative	144	101	245	18.2	27	17	22	39	5	Has been very apathetic and weak since operation and steadily growing more so, died while blood was being drawn

Necropsy tissue found: General postmortem examination entirely negative. No ulceration of the gastric or duodenal mucosa. Died thirty hours after bilateral suprarenalectomy. No necessary suprarenal

PROTOCOL 11—Dog 16 Female, weighed 71 kg

Date	Actual Readings					Change from Preoperative Average Calculated in Relation to Blood Solids				Remarks
	Mg Cholesterol per 100 C e Blood			Blood Solids, per Blood		Mg Cholesterol per 100 C e Blood			Blood Urea	
	Free	Ester	Total	Cent	Urea	Free	Ester	Total		
2/4/24										Dog put on constant diet
2/5/24	176	96	272	20.1	16					Lively, condition good, appetite good
2/6/24	177	91	268	20.0						Lively, condition good, appetite good
2/7/24	179	89	268	19.2	14					Lively, condition good, appetite good
2/8/24	180	92	272	19.2						Lively, condition good, appetite good
Preoperative average 2/9/24	178	92	270	19.6	15					Operation bilateral suprarenalectomy at 9:30 a.m.
2/9/24 6 hours postop- erative	175	91	266	18.1		14	7	21		Weak and apathetic, did not respond to calling
2/9/24 12 hours postop- erative	171	101	272	19.6	35	-7	9	2	21	Weakness and apathy more marked, raises head when called but would not walk

Necropsy: General postmortem examination negative except for some small areas of questionable pneumonia in the bases of the lungs and some very unusually large lymph nodes (mesenteric) in the region of the appendix. No accessory suprarenal tissue found. No ulceration of the gastric or duodenal mucosa. Not pregnant. Sections made of lung, liver and mesenteric lymph node show no pathological changes. Died eighteen hours after bilateral suprarenalectomy.

## PROTOCOL 12—Dog 45 Female, weighed 56 kg

Date	Actual Readings					Change from Preoperative Average Calculated in Relation to Blood Solids				Remarks
	Mg Cholesterol per 100 C c Blood			Blood Solids, per Cent	Blood Urea	Mg Cholesterol per 100 C c Blood			Blood Urea	
	Free	Ester	Total			Free	Ester	Total		
1/15/24										Dog put on constant diet
1/19/24	143	49	192	21 0	23					Lively and active, appetite excellent
1/21/24	125	57	182	20 7	16					Lively and active, appetite excellent
1/22/24	127	51	178	20 4						Lively and active, appetite excellent
Preoperative average	132	52	184	20 7	19					
1/23/24										Operation bilateral suprarenalectomy at 2 p m
1/24/24 18 hours postop- erative	190	55	245	21 8	17	51	0	51	—1	Apathetic but not mark- edly weak, could walk short distances
1/24/24 30 hours postop- erative	183	48	231	21 5	49	46	—6	40	31	Apathetic and much weaker, struggled while being bled, died about five hours after this phlebotomy

Necropsy General postmortem examination negative except for a very early pregnancy. Each ovary showed from three to four fairly large corpora luteum. No accessory suprarenal tissue found. No ulceration of the gastric or duodenal mucosa. Sections made from the uterine horns showed an early pregnancy. Died thirty six hours postoperative.

## PROTOCOL 13—Dog 46 Female, weighed 110 kg

Date	Actual Readings					Change from Preoperative Average Calculated in Relation to Blood Solids				Remarks
	Mg Cholesterol per 100 C c Blood			Blood Solids, per Cent	Blood Urea	Mg Cholesterol per 100 C c Blood			Blood Urea	
	Free	Ester	Total			Free	Ester	Total		
1/28/24										Dog put on constant diet
1/30/24	145	69	214	20 7	10					Lively, taking diet well
1/31/24	150	77	227	20 1	10					Lively, taking diet well
2/ 1/24	148	71	219	20 2						Lively, taking diet well
Preoperative average 2/ 1/24	148	72	220	20 3	10					Operation bilateral suprarenalectomy
10 hours postop- erative	157	86	243	20 3	31	9	14	23	21	Apathetic and weak, walked a few steps when called and then sank to the floor, died about six hours after this phle- botomy

Necropsy General postmortem examination negative. No ulceration of the gastric or duodenal mucosa. No accessory suprarenal tissue found. Not pregnant. Died sixteen hours postoperative.

Unilateral suprarenalectomies were performed in three dogs. Dog 30 died three days after operation from a rather extensive pneumonia. Although it has been reported that pneumonia and the acute infections cause a lowering of the blood cholesterol,<sup>6, 22, 23</sup> this dog showed a

22 Weltman, O. Ueber das doppeltbrechende Lipoid der Nebenniere, Beitr z path Anat u z allg Path **56** 278-324, 1913

23 Denis, W. Blood Cholesterol under Pathological Conditions, J Biol Chem **29** 93-110 (Feb) 1917

definite rise This increase was evenly divided between the free and combined cholesterol (Protocol 14)

PROTOCOL 14—Dog 30 Female, weighed 70 kg

Date	Actual Readings					Change from Preoperative Average Calculated in Relation to Blood Solids				Remarks
	Mg Cholesterol per 100 C e Blood			Blood Solids, per Cent	Blood Urea	Mg Cholesterol per 100 C e Blood			Blood Urea	
	Free	Ester	Total			Free	Ester	Total		
11/18/23										Dog put on constant diet
11/21/23	102	79	181	14.2	21					Active, appetite good, condition good
11/22/23	103	79	182	14.6	26					Active, appetite good, condition good
11/23/23	104	82	186	14.9						Active, appetite good, condition good
11/25/23										Quieter than usual, appe- tite good, weight, 67 kg, moderate discharge from eyes and nose
Preoperative average 11/26/23	103	80	183	14.6	24					
11/27/23 24 hours postop- erative	123	94	217	15.9	16	11	7	18	—10	Operation left supra- renalectomy at 3 p.m. Not fed today, drowsy and apathetic but re- sponded quickly when called, has a cold, eyes and nose running pro- fusely
11/28/23 48 hours postop- erative 11/29/23	124	110	225	14.2	41	24	28	47	18	Very drowsy, marked purulent discharge from nose and eyes, appetite very poor Has eaten practically nothing since operation, drowsy and very weak, eyes and nose still run- ning profusely, dis- charge is purulent, died in the afternoon about 72 hours postoperative

Necropsy Lungs showed an extensive pneumonia throughout the right lower and middle lobes. Heart normal. Gastrointestinal tract normal. Genito-urinary organs negative. Right suprarenal did not appear abnormal.

Died seventy-two hours after a unilateral suprarenalectomy from pneumonia.

The other two dogs (1 and 14) showed very definite elevations of the blood cholesterol following the removal of one suprarenal. In these two experiments the blood was examined at first every day, then every third day, and finally once a week for periods of ten and ten and one-half weeks, respectively. In neither case did the blood cholesterol return to normal but remained well elevated during the entire period, although the highest figure was reached in both cases at about the second week postoperatively. After the removal of the remaining suprarenal both animals showed a tendency to a still further increase over the last reading following the unilateral suprarenalectomy. In both dogs the increase in the free cholesterol was more marked than that of the esters. There was no definite increase in the blood urea in either case. The blood solids showed a tendency to decrease. The duration of life following the removal of the second suprarenal was twenty-two and eighteen hours, respectively (Protocols 15 and 16).

## PROTOCOL 15—Dog 1 Female, weighed 51 kg

Date	Actual Readings					Change from Preoperative Average Calculated in Relation to Blood Solids				Remarks
	Mg Cholesterol per 100 C c Blood			Blood Solids, per Cent	Blood Urea	Mg Cholesterol per 100 C c Blood			Blood Urea	
	Free	Ester	Total			Free	Ester	Total		
11/30/23										Dog put on constant diet
12/ 2/23	106	75	181	20.2	19					Lively and active, appetite excellent
12/ 3/23	110	61	171	20.5	13					Lively and active, appetite excellent
12/ 4/23	124	61	185	19.9						Lively and active, appetite excellent
Preoperative average	113	66	179	20.3	16					
12/ 5/23										Operation right supra-renalaeotomy
12/ 6/23	131	79	210	19.8	17	21	15	36	1	Active, responds to call, condition good, not fed
12/ 7/23	122	73	195	18.5		19	13	32	—	Active, condition excellent, appetite excellent
12/ 8/23	136	89	225	18.0	12	36	30	66	—2	Active, appetite and condition excellent
12/10/23	144	83	227	17.1	14	49	27	76	0	Active, appetite and condition excellent, weight, 4.8 kg
12/13/23	148	95	243	18.5	13	45	35	80	—2	Active, appetite and condition excellent
12/16/23	164	91	255	19.1		57	29	86		Active, appetite and condition excellent, weight, 4.5 kg
12/19/23	155	74	229	19.2	20	48	12	60	5	Active, appetite and condition excellent
12/22/23	157	79	236	19.3	14	50	16	66	—1	Active, appetite and condition excellent
12/26/23	143	88	231	19.4		35	25	60		Active, appetite and condition excellent, weight, 4.5 kg
12/29/23	155	88	243	18.9	12	50	26	76	—2	Active, appetite and condition excellent
1/ 2/24	159	81	240	19.0		53	19	72		Active, appetite and condition excellent
1/ 8/24	144	77	221	19.1	20	37	15	52	5	Active, appetite and condition excellent
1/15/24	136	85	221	19.8	21	26	21	47	5	Active, appetite and condition excellent
1/22/24	137	80	217	20.0	13	26	15	41	—3	Active, appetite and condition excellent
1/29/24	144	72	216	19.4	16	36	9	45	1	Active, appetite and condition excellent
2/ 5/24	135	77	212	19.6		26	13	39		Active, appetite and condition excellent
2/12/24	141	69	210	19.6		32	5	37		Active, appetite and condition excellent
Average increase in 10 weeks following unilateral suprarenalectomy						38	19	57		
2/13/24										Operation left supra-renalaeotomy
6 hours postop- erative	139	64	203	17.8	16	40	6	46	2	Moderate weakness, responds to call, can walk
12 hours postop- erative	133	68	201	18.5	18	30	8	38	3	Moderate weakness, responds to call, walking
22 hours postop- erative	147	70	217	18.6		44	9	53	—	Walking and responded to calling, died immediately after phlebotomy although the dog's condition before this procedure seemed to be fairly good, no struggling during the bleeding

Neeropsy General postmortem examination entirely negative No accessory suprarenal tissue found No gastric or duodenal ulcers Not pregnant  
Died twenty-two hours after removal of the second suprarenal gland

## PROTOCOL 16—Dog 14 Female, weighed 48 kg

Date	Actual Readings					Change from Preoperative Average Calculated in Relation to Blood Solids				Remarks
	Mg Cholesterol per 100 C c Blood			Blood Solids, per Cent	Blood Urea	Mg Cholesterol per 100 C c Blood			Blood Urea	
	Free	Ester	Total			Free	Ester	Total		
11/18/23										Dog put on constant diet
11/20/23	114	65	179	21.3	15					Lively, appetite and con- dition excellent
11/23/23	101	69	170	22.2	29					Lively, appetite and con- dition excellent
11/28/23	102	72	174	20.3	19					Lively, appetite and con- dition excellent, weight, 46 kg
Preoperative average	106	69	175	21.3	21					
11/30/23										Operation right supra- renalectomy
12/ 1/23	125	73	198	20.7		22	6	28		Fairly lively, condition good, not fed today
12/ 2/23	153	78	231	19.7	12	55	14	69	-7	Lively, appetite and con- dition excellent
12/ 3/23	133	65	198	17.7	14	45	7	52	-3	Lively, appetite and con- dition excellent
12/ 5/23	137	73	210	18.9		43	12	55		Lively, appetite and con- dition excellent
12/ 7/23	154	86	240	18.5	20	62	26	88	2	Lively, appetite and con- dition excellent
12/10/23	145	86	231	18.4	19	53	27	80	1	Lively, appetite and con- dition excellent, weight, 41 kg
12/13/23	144	85	229	18.4	10	52	26	78	-8	Lively, appetite and con- dition excellent
12/16/23	164	91	255	19.7		66	27	93		Lively, appetite and con- dition excellent, weight, 40 kg
12/19/23	146	85	231	19.5	19	49	22	71	0	Lively, appetite and con- dition excellent
12/22/23	137	96	233	19.5	19	40	33	73	0	Lively, appetite and con- dition excellent
12/26/23	120	73	193	18.8	16	27	12	39	-3	Lively, appetite and con- dition excellent
12/29/23	152	91	243	18.8	23	59	30	89	4	Lively, appetite and con- dition excellent
1/ 2/24	161	84	245	19.6		64	21	85		Lively, appetite and con- dition excellent
1/ 8/24	133	92	225	18.9	13	39	31	70	-6	Lively, appetite and con- dition excellent
1/15/24	134	87	221	19.3	15	38	25	63	-4	Lively, appetite and con- dition excellent
1/22/24	138	85	223	20.0	19	39	20	59	-1	Lively, appetite and con- dition excellent
1/29/24	150	73	223	19.0	12	55	12	67	-7	Lively, appetite and con- dition excellent
2/ 5/24	140	87	227	19.2		44	25	69		Lively, appetite and con- dition excellent
2/12/24	133	92	225	18.6		41	32	73		Lively, appetite and con- dition excellent
Average increase in 10½ weeks following unilateral suprarenalectomy 2/12/24						46.5	21.5	68	-3	Operation left supra- renalectomy, moderate hypertrophy of gland
8 hours postop- erative	156	89	245	18.3		45	30	95		Moderate weakness, re- sponds to calling, walks slightly
18 hours postop- erative	156	73	229	21.3	18	50	4	54	-3	Marked weakness and apathy, does not re- spond or walk died almost immediately after the phlebotomy

Neeropsy General postmortem examination entirely negative No necessary suprarenal tissue found No gastric or duodenal ulcer Not pregnant  
Died eighteen hours after removal of the second suprarenal gland

Horiuchi<sup>24</sup> and Boggs and Morris<sup>25</sup> have described a lipemia in rabbits, produced by continued frequently repeated bleedings. Bloor<sup>26</sup> found that this condition was readily produced in rabbits but not in dogs. In order to observe the effects of the repeated small bleedings, such as were necessary in our experiments, and a prolonged Cowgill diet, Dog 6 was used as a control. This animal was kept on a constant diet for a month and during this time the usual small bleedings were made.

PROTOCOL 17—Dog 6 Male, weighed 57 kg

Date	Actual Readings					Change from Preoperative Average Calculated in Relation to Blood Solids			Remarks
	Mg Oolesterol per 100 O c Blood			Blood Solids, per Cent	Blood Urea	Mg Oolesterol per 100 O c Blood			
	Free	Ester	Total			Free	Ester	Total	
	Free	Ester	Total	Free	Ester	Total			
1/10/24									Dog put on constant diet
1/11/24	132	63	195	21.8	11				Lively, taking diet well
1/13/24	134	55	189	21.0					Lively, taking diet well
1/16/24	138	44	182	20.3					Lively, appetite fair
1/19/24	134	51	185	19.9					Lively, appetite excellent
1/21/24	136	55	191	19.4	14				Lively, appetite and condition excellent
1/25/24	132	51	183	19.4					Lively, appetite and condition excellent
1/28/24	126	46	172	19.2					Lively, appetite and condition excellent
1/30/24	127	51	178	19.2	12				Lively, appetite good, weight, 53 kg
2/ 1/24	128	46	174	19.1					Lively, appetite good, condition good
2/ 4/24	133	41	174	19.2					Lively, appetite poor, condition fair but a marked diarrhea is present
2/ 8/24	132	46	178	19.3					Appetite poor, diarrhea more marked, still very active and lively, and general condition appears to be fairly good
2/11/24	131	39	170	21.4					Appetite poor, diarrhea about the same, general condition poor
Preoperative average	132	49	181	19.9	12				
2/11/24									Operation bilateral suprarenal- ectomy at 2 p m
2/11/24 6 hours postop- erative	132	39	171	21.8		-13	-15	-28	Weak and somewhat apathetic, can walk only a few steps at a time, diarrhea very marked, stools slightly blood streaked
2/11/24 10 hours postop- erative	139	44	183	21.8		-6	-11	-16	Very weak, semicomatose, died about one half hour after the phlebotomy

Neeropsy General postmortem examination negative except for intestinal mucosa which showed very marked degree of congestion and edema from just beyond the pylorus down to the sigmoid. No ulceration present. Mesenteric lymph nodes near the appendix were markedly enlarged. Stomach appeared normal. No accessory suprarenal tissue found. Died about ten and one half hours after bilateral suprarenal-ectomy.

24 Horiuchi, Y. Studies on Blood Fat. I Variations of the Blood Fat Constituents of Rabbits under Normal Conditions, *J Biol Chem* **44** 345-361 (Nov) 1920, Studies on Blood Fat II Lipemia in Acute Anemia, *J Biol Chem* **44** 363-379 (Nov) 1920.

25 Boggs, T. R., and Morris, R. S. Experimental Lipemia in Rabbits, *J Exper Med* **11** 553-560, 1909.

26 Bloor, W. R. Blood Phosphates in the Lipemia Produced by Acute Experimental Anemia in Rabbits, *J Biol Chem* **45** 171-187 (Dec) 1920.



from the jugular vein every second or third day For the first three weeks of the experiment the dog was in excellent condition, and the blood cholesterol showed very little variation from day to day except a tendency toward a slight drop together with the blood solids

At about this time, however, the dog developed anorexia and a rather severe diarrhea As the diarrhea became more marked it was decided to perform a bilateral suprarenalectomy although the dog's general condition was poor The animal stood the operation badly and died about ten hours later During this short period the diarrhea was extremely marked and the stools were blood streaked In this case a definite drop in the blood cholesterol was noted following the bilateral suprarenalectomy, but it should be considered that the dog was quite sick and abnormal at the time of operation Luden<sup>11</sup> has reported that a drop occurs in the blood cholesterol following an attack of diarrhea (Protocol 17)

#### THE EFFECT OF EPINEPHRIN ON THE BLOOD CHOLESTEROL

The effect of epinephrin on the cholesterol content of the blood was studied in three dogs Readings were made just before the injection of the drug and at intervals varying from fifteen minutes to an hour and a half after its injection In Dogs 40 and 41 the injection was given intravenously and in Dog 42 it was given subcutaneously In none of the animals was there any definite change noted in either the blood cholesterol or the hemoglobin (Protocols 18, 19 and 20)

##### PROTOCOL 18—*Dog 40 Female, weighed 13.8 kg*

Two cubic centimeters of epinephrin (1:1000) was injected intravenously immediately after the first blood specimen was obtained

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	Mg Cholesterol per 100 Cc Blood	Hemoglobin Per Cent
Before injection of epinephrin	161	114
15 minutes after injection of epinephrin	153	119
45 minutes after injection of epinephrin	154	117
75 minutes after injection of epinephrin	162	114

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##### PROTOCOL 19—*Dog 41 Male, weighed 13 kg*

Two cubic centimeters of epinephrin (1:1000) was injected intravenously after the first blood specimen was obtained

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	Mg Cholesterol per 100 Cc Blood	Hemoglobin Per Cent
Before injection of epinephrin	157	117
30 minutes after injection of epinephrin	156	121
60 minutes after injection of epinephrin	154	119

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## PROTOCOL 20—Dog 42 Male, weighed 15 kg

Two cubic centimeters of epinephrin (1 1000 was injected subcutaneously after the first blood specimen was obtained

	Mg Cholesterol per 100 Cc Blood	Hemoglobin Per Cent
Before injection of epinephrin	177	105
30 minutes after injection of epinephrin	174	108
60 minutes after injection of epinephrin	173	110
90 minutes after injection of epinephrin	178	108

## THE EFFECT OF SUPRARENAL EXTRACT ON THE BLOOD CHOLESTEROL

Extracts of fresh pigs' suprarenal glands were made following, more or less, the method of extraction described by Collip for the preparation of insulin<sup>27</sup> The various extracts were injected intravenously into five dogs In none of these dogs was there any definite change noted in the cholesterol content of the blood or the hemoglobin The extracts were apparently very toxic causing marked symptoms and death in four of the dogs This was probably due to the cholin which is present in suprarenal extracts<sup>28</sup> (Protocols 21, 22, 23, 24 and 25)

## PROTOCOL 21—Dog 49 Male, weighed 90 kg

300 gm of pig's suprarenal were extracted in the following way

- 1 Thoroughly minced and mixed with an equal volume of 95 per cent alcohol and allowed to stand from 4 to 5 hours with frequent stirring
- 2 Filtered through gauze and squeezed out and then filtered clear through filter paper
- 3 Two volumes of 95 per cent alcohol added to the filtrate and allowed to stand over night to allow for precipitation of the proteins
- 4 Filtered and the filtrate evaporated to a very small volume with a current of air
- 5 Made up to an aqueous solution with 200 cc of distilled water
- 6 Washed twice in a separatory funnel with ether until test showed it to be cholesterol free Oxygen bubbled through extract for thirty minutes in order to decompose the epinephrin

Twenty cubic centimeters (equivalent of 30 gm of suprarenal) of this extract was injected intravenously into a dog after having drawn the first blood sample

	Mg Cholesterol per 100 Cc Blood	Hemoglobin Per Cent
Before injection of extract	210	120
½ hour after injection of extract	203	116
1¼ hour after injection of extract	201	116
2 hours after injection of extract	203	112

27 Allen, F M Summary on Publications on Insulin, J Metabolic Res 2 125-140, 1922

28 Biedl, A Innere Sekretion, Urban u Schwartzenberg, Berlin, 1910, pp 254-257

Almost immediately after the extract was injected, there was a period of apnea and dog went into a semicomatose condition which lasted for about three hours when the animal died. During this time respirations were shallow and rapid. Mucous membranes were definitely cyanotic. Profuse nasal secretion.

**Necropsy** The heart showed subpericardial, myocardial, and subendothelial hemorrhages. The lungs were essentially normal. Esophagus normal. Aorta normal. Stomach showed severe hemorrhages into the mucous membranes and large clots in its cavity. There were marked submucous hemorrhages into the rest of the gastro-intestinal tract down to the rectum except for about 4 inches on either side of the ileocecal junction. Spleen markedly enlarged, weight 80 gm bluish purple in color and on section was markedly hemorrhagic. Liver usual size but had definite hemorrhages into it. Kidneys markedly congested but not hemorrhagic. Bladder normal. Brain sub-arachnoid and subpial hemorrhages. Suprarenals normal.

PROTOCOL 22—Dog 50 Male, weighed 70 kg

The extract described under Dog 40 (Protocol 21) was purified according to Collip's insulin method in the following way:

The watery extract was evaporated to a very small volume by means of a current of air. To this was added 80 per cent alcohol and then the solution centrifugated for one-half hour at a high speed. No four layers, as described by Collip, developed. However, the entire clear solution was delivered into several volumes of 95 per cent alcohol and precipitation allowed to take place over night. The filtrate was then evaporated to dryness by means of a current of air and the residue taken up with 100 cc of distilled water. The precipitate was taken up with 10 cc of distilled water.

The 10 cc of distilled water containing the before mentioned precipitate was injected intravenously after withdrawing the first blood sample. The dog's respirations immediately became very slow and shallow, pulse became irregular, rate 80. The dog became very drowsy and remained so for several hours. However, the pulse and respirations returned to normal in about twenty minutes. The dog seemed to have completely recovered in about four hours.

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	Mg Choles- terol per 100 Cc Blood	Hemoglobin Per Cent
Before injection of extract	207	148
½ hour after injection of extract	201	140
1¼ hour after injection of extract	197	134
2 hours after injection of extract	193	138

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PROTOCOL 23—Dog 51 Male, weighed 10 kg

This dog received 15 cc of the extract (equivalent to about 45 gm of suprarenal) obtained from the before described filtrate (Protocol 22) intravenously. It was followed by irregular, shallow respirations for only a short period, and a rapid pulse. The mucous membranes became somewhat cyanotic, the pupils very much dilated. Dog was somewhat drowsy and nonresponsive but this seemed to clear up after several hours. However, the dog was found dead the next morning. No necropsy was performed.

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	Mg Choles- terol per 100 Cc Blood	Hemoglobin Per Cent
Before injection of extract	291	120
½ hour after injection of extract	288	124
1½ hour after injection of extract	294	124

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PROTOCOL 24—Dog 52 Female, weighed 13 kg

Twenty cubic centimeters of the same filtrate as that used for Dog 51 (Protocol 23) was boiled for about fifteen minutes. This was then cooled and injected intravenously into the dog. Before injection, the dog's pulse was 120,

respirations 16 A few minutes after injection the respirations became rapid and shallow for about one minute and then very deep and slow (from 2 to 3 per minute) The pulse became so rapid that it could not be counted Dog evidently lost consciousness, pupils were widely dilated and the membranes definitely cyanotic After about five minutes the pulse went from 100 to 110 and the respirations reached about 10 or 12 and remained so until death which took place thirty minutes after the injection During this entire period the dog remained semicomatose and about five minutes before death respiration became very labored and irregular and bloody, frothy fluid escaped from the nostril in large quantities

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	Mg Cholesterol per 100 Cc Blood	Hemoglobin Per Cent
Before injection of extract	207	124
½ hour after injection of extract	201	120

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Necropsy Muscles very dark red in color Heart also dark, numerous subpericardial hemorrhages present and also a few intracardial and subendocardial hemorrhages present Trachea was filled with very frothy, slightly blood tinged fluid The lungs showed a definite edema to be present and were markedly congested The stomach was full of food and only very slight submucosal hemorrhages were present The small and large intestines showed a moderate degree of submucosal hemorrhages The uterus and tubes were normal, suprarenals normal Kidneys markedly cyanotic with a congested cortex and a rather pale medulla No hemorrhages Bladder normal Liver congested and dark Spleen only slightly congested

PROTOCOL 25—Dog 58 Male, weighed 14 kg

One hundred and twenty grams of pigs' suprarenal glands were thoroughly minced An equal volume of 95 per cent alcohol was added and the mixture allowed to stand for several hours with frequent stirring Filtered and then the filtrate was evaporated to almost dryness with a current of air This was then taken up in 60 cc of distilled water and filtered again

Fifteen cubic centimeters of this filtrate (equivalent of 30 gm of suprarenal) was injected intravenously into the dog after the first blood specimen had been obtained This caused no apparent change in the dog's general condition during the hour and a half that he was observed after the injection of the extract but he was found dead in his cage the next morning Unfortunately, the animal was thrown out by mistake and therefore no necropsy was done

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	Mg Cholesterol per 100 Cc Blood	Hemoglobin Per Cent
Before injection of the extract	195	120
½ hour after injection of the extract	191	118
1 hour after injection of the extract	192	120
1½ hour after injection of the extract .	198	117

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COMMENT

In our experiments, an increase in the blood cholesterol was noted in every case after removal of one or one and a half suprarenals, but removal of the remaining suprarenal did not consistently raise the blood cholesterol still further Of the nine uncomplicated bilateral supra-renalectomies (Dog 6 excluded) done in one stage, a very definite elevation of the blood cholesterol was noted in six of the experiments, slight

elevations of 10 per cent or less in two, and practically no change in one. These findings agree more or less with those reported by Rothschild<sup>4</sup> but are unlike those of Grigaut,<sup>6</sup> who found a hypercholesterinemia after unilateral but not after bilateral suprarenalectomies, and those of Baumann and Holly<sup>7</sup> who report no change in the blood cholesterol of rabbits after either a unilateral or bilateral suprarenalectomy. Neither did we observe "the latent period" which Grigaut describes following unilateral suprarenalectomy but instead found an almost immediate rise in the blood cholesterol in practically every case. No constant curve of the hypercholesterinemia following suprarenalectomy could be plotted, as the highest figures were obtained at varying intervals postoperatively. However, in the two unilateral suprarenalectomy experiments which were followed for long periods the most marked hypercholesterinemia was observed at about two weeks after the operation.

The ratio between the increase in the free and combined cholesterol was not constant but the rise was usually more marked in the case of the free cholesterol. This is consistent with the fact that normally there is about twice as much free cholesterol as cholesterol-ester present in whole blood.<sup>29</sup>

From these results it is not possible to draw any definite conclusions as to the exact rôle of the suprarenal in cholesterol metabolism, although it seems quite certain that some relationship does exist between the two. The hypercholesterinemia which occurs after a complete extirpation of the suprarenal glands is strongly against the theory of the French investigators that this organ secretes cholesterol. The German idea that the suprarenals act as a storehouse for cholesterol also seems improbable because of their small size in relation to the rest of the body. Their cholesterol content, though proportionally high for their weight, can represent but a small amount of all the cholesterol present in the entire organism.

It may be possible that the internal secretion of the suprarenal has some effect on the blood cholesterol similar to that of the pancreas on the blood sugar. Alessandri<sup>30</sup> reports increases of over 10 per cent within a half hour in six out of ten patients in whom he injected epinephrin subcutaneously or intravenously. In our experiments on dogs, we observed no change in the blood cholesterol as a result of the injection of this drug either subcutaneously or intravenously (Protocols 18, 19 and 20). Neither could we influence the cholesterol content of the blood by the injections of large doses of extracts of pigs' fresh suprarenal glands (Protocols 21, 22, 23, 24 and 25). It is possible,

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29 Bloor, W. R., and Knudson, A. Cholesterol and Cholesterol-Esters in the Human Blood, *J Biol Chem* **29**:7-13 (Feb.) 1917.

30 Alessandri, C. Cholesterol Content of the Blood, *Riforma med* **37** 1095-1099 (Nov.) 1921.

however that the method of extraction which we used (Collip's insulin method) is not adapted to bring out the active principle which we were trying to obtain

The blood sugar showed no constant variation in these experiments but it usually dropped after operation. Our studies of the changes of the blood urea or nonprotein nitrogen following complete extirpation of the suprarenals revealed a marked increase in these substances in a large majority of the experiments. This phenomenon has been previously studied by Marshall and Davis<sup>31</sup>. They found that there was a decreased nitrogen excretion in the urine which was accounted for by nitrogen retention and therefore, probably no marked change occurred in the protein catabolism. This definite lowering of kidney efficiency occurred with a normal blood pressure and while the animals were still in good general condition. Histologically, the kidneys showed no changes. The authors suggest that the suprarenals may secrete some substance necessary for the maintenance of normal kidney function.

The blood solids were, as a general rule, increased in our animals immediately after operation but this was not so in all of the experiments. The increases which we did find were not as marked as those reported by Donath<sup>13</sup>.

Although several investigators have reported ulceration occurring in the gastric mucosa quite constantly after bilateral suprarenalectomy,<sup>32</sup> none was observed in any of our dogs.

#### SUMMARY

The blood cholesterol, blood urea or nonprotein nitrogen, blood sugar and blood concentration were studied before and after operation in dogs which were kept on a carefully calculated constant diet. A majority of the animals that had a bilateral suprarenalectomy done in one stage showed a hypercholesterinemia following the operation. Removal of one or one and a half suprarenals caused an increase in the blood cholesterol in every instance. No consistent findings were observed in

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31 Marshall, E. K., and Davis, D. M. The Influence of the Adrenals on the Kidneys, *J. Pharmacol. & Exper. Therap.* **8**: 525-550, 1916.

32 Gibelli, C. (cited by Mann). La funzione delle capsule surrenali in rapporto col processo di riparazione delle fratture e coll' eziologia dell' ulcera gastrica. *Pathologica* **1**: 131, 1909. Finzi, O. Ueber Veränderungen der Magenschleimhaut bei Tieren nach Nebenneurenextirpation und über experimentell erzeugte Magenschwüre, *Virchows Arch. f. path. Anat.* **224**: 413-432, 1913. Friedman, G. A. The Production of Gastric Lesions and Ulcers in Rabbits by Extirpation of the Adrenals, *Proc. Soc. Exper. Biol. and Med.* **11**: 169-171, 1914. The Influence of Removal of the Adrenals and One-sided Thyroidectomy Upon the Gastric and Duodenal Mucosa; the Experimental Production of Lesions, Erosions and Acute Ulcers. *J. M. Res.* **32**: 287-307, 1915. Mann, F. C. Gastric Ulcer Following Excision of Adrenals, *J. Exper. Med.* **23**: 203-208 (Feb.) 1916. *ibid.*, **24**: 329-332 (Oct.) 1916.

the blood sugar determinations In a large majority of the animals, bilateral suprarenalectomy resulted in a definite rise in the blood urea or nonprotein nitrogen The blood concentration was usually increased after operation Injections of epinephrin or extracts of pigs' fresh suprarenal glands did not influence the blood cholesterol

# THE TREATMENT OF PNEUMONIAS IN CHILDREN

A REPORT TO DATE ON OUR EXPERIMENTAL AND CLINICAL RESULTS, USING THE BLOOD AND SERUM OF CHICKENS<sup>†</sup>

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AND

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In a previous communication,<sup>1</sup> we took up in detail the theory of using the blood or blood serum of fowls in the treatment of pneumonia in children

It is the object of this paper to present the results of our work, both with laboratory animals, and with children in whom pneumonia was treated with the blood or serum of fowls, mostly chickens

After the first season's work (from 1921 to 1922), a study of the literature was made, and the work of Bull and McKee,<sup>2</sup> and that of Keyes<sup>3</sup> was found

We attempted to repeat the experiments of Bull and McKee, but our results were much less striking than were theirs, possibly because we allowed our serum to age too much, it was suggested that in this mode of procedure much of the antibody in the serum was perhaps destroyed by the host before the pneumococcus was injected. We, therefore, started another group of experiments, reversing the order, that is, making the pneumococcic injection first and following this with varying doses and at varying intervals with the chicken serum. These results were then checked with other groups where, instead of chicken serum, were employed fresh human blood serum, aged human blood serum, the serum from chickens that had been given injections of virulent pneumococcus culture intraperitoneally (with a proved agglutinating power), pneumolin<sup>4</sup> and commercial antipneumococcic serum

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<sup>†</sup> Read before the Kansas City Academy of Medicine, April 4, 1924

<sup>†</sup> From the wards of the Childrens' Mercy Hospital, and the laboratories of the Kansas City General Hospital

1 Berger, H C, and Montgomery, J G. The Use of Chicken Blood in the Treatment of Pneumonias in Children. A Preliminary Report, J Missouri State M A **20** 81 (March) 1923

2 Bull, C G, and McKee, C M. Antipneumococcus Protective Substances in Normal Chicken Serum, Am J Hygiene **1** (May) 1921

3 Keyes, P. The Natural Resistance of the Pigeon to the Pneumococcus, J Infect Dis **18** 277, 1916, Production of Antibodies to Pneumococci in an Insusceptible Host, J A M A **56** 1878 (June 24) 1911

4 Pneusolin, according to the statement of the manufacturing laboratory (H K Mulford Company), is "an aqueous solution of active immune bodies extracted from antipneumococcus serum, Types 1, 2 and 3 combined. It is polyvalent and is practically free from horse serum protein."



In our clinical work, we were at first forced to use the whole blood of the chicken, as stated in our preliminary report<sup>1</sup>. After we were able to procure serum we used it exclusively, abandoning the use of the whole blood because the serum was safer, easier to administer, always available, more comfortable to the patient, and could be administered in larger dosage and intravenously, whereas the whole blood was always given intramuscularly or hypodermically. Even with the greatest care we had some abscesses resulting from the injections of the blood, partially, we think, due to pressure, owing to the rapidity with which it had to be given.

TABLE 1—*Agglutination Power of Serum, Type 1*

No	Serum	11	12	13	14	15	16	17	18	19	1-10	1-11	1-12	1-13	1-14	1-15
1	Agglutinating	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+
2	Anti Pn I	1+	1+	1+	±	±	—	—	—	—	—	—	—	—	—	—
3	Anti-Pn Poly	±	±	—	—	—	—	—	—	—	—	—	—	—	—	—
4	Imm Ch I	4+	3+	3+	2+	2+	2+	2+	2+	2+	2+	+	+	+	+	+
5	Imm Ch II	+	+	+	±	±	±	±	±	±	±	±	—	—	—	—
6	Imm Ch III	2+	2+	2+	2+	+	+	+	+	+	+	±	±	—	—	—

- 1 Agglutinating serum Type I, from N Y State Board of Health  
 2 and 3 Lederle's antipneumococcus serum, Type I and polyvalent  
 4 5 and 6 Immune serum prepared by injecting chickens intraperitoneally with Type 1 pneumococcus cultures  
 4 One injection, bled in eight days  
 5 Two injections at intervals of eight days bled in seven days after last injection  
 6 Three injections at intervals of eight and seven days, bled in fourteen days  
 Readings made after two hours in 37 C water bath followed by eight hours in icebox

TABLE 2—*Agglutination Power of Serum, Type 2*

No	Serum	11	12	13	14	15	1-6	1-7	18	19	1-10	1-11	1-12	1-13	1-14	1-15
1	Agglutinating	4+	4+	4+	4+	4+	4+	4+	2+	2+	±	±	±	—	—	—
2	Anti Pn Poly	3+	3+	2+	+	—	—	—	—	—	—	—	—	—	—	—
3	Immune Ch I	4+	3+	2+	2+	2+	2+	+	+	+	±	—	—	—	—	—
4	Immune Ch III	2+	2+	+	+	+	±	±	—	—	—	—	—	—	—	—
5	Normal Ch	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
6	Pneusolin	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
7	Aged human	—	No other dilutions run													

- 1 Agglutinating serum (diagnostic) from N Y State Board of Health  
 2 Lederle's polyvalent antipneumococcus serum (therapeutic)  
 3 Immunized chicken serum prepared by injecting 15 cc of heavy pneumococcus Type II culture into peritoneal cavity, bled in eight days  
 4 Immunized chicken serum prepared as above but with a second injection of 25 cc in eight days, third in seven days, bled after fourteen days  
 5 Normal aged chicken serum obtained by bleeding and withdrawing serum  
 6 Mulford's pneumolin  
 7 Aged human serum  
 Readings taken after two hours in 37 C water bath and twelve hours in icebox

Table 1 shows the agglutinating power of the agglutinating serum Type 1 from the New York State Board of Health, which was 4 plus in dilutions up to 1 15, of antipneumococcic serum Type 1 (Lederle commercial secured on the local market), which was 1 plus in dilutions up to 1 3, and ± in dilutions of 1 4 and 1 5, of antipneumococcic serum polyvalent (Lederle), which was ± in dilutions up to 1 2, of the serum prepared by injecting chickens intraperitoneally with Type 1 pneumococcus culture and bleeding eight days later, which was 4 plus in a dilution of 1 1, 3 plus in a dilution of 1 2 and 1 3 and 2 plus in

dilutions from 1 4 up to 1 10, and plus in dilutions of 1 11 up to 1 15, of the serum from chickens injected as above, but having a second injection eight days after the first and being bled seven days after the last injection which was plus in dilutions of 1 1 up to 1 3,  $\pm$  in dilutions of 1 4 up to 1 10 and minus thereafter, of a third group of chickens having two injections as the previous chickens, a third injection seven days later and bled fourteen days after the last injection which was 2 plus in dilutions of 1 1 up to 1 4, and plus in dilutions of 1 5 up to 1 10, and  $\pm$  in dilutions of 1 11 and 1 12, and minus thereafter. The readings were made after two hours in a water bath at 37 C (98.6) followed by eight hours in the icebox.

This experiment (Table 2) was made to show the agglutinating power to the Type 2 pneumococcus of the diagnostic agglutinating serum of the New York State Board of Health, which was 4 plus in dilutions up to 1 7, 2 plus in dilutions of 1 8 and 1 9, and  $\pm$  in

TABLE 3—*Agglutination Power of Serum, Type 3*

No	Serum	1 1	1 2	1 3	1 4	1 5	1 6	1 7	1 8	1 9	1 10	1 11	1 12	1 13	1 14	1 15
1	Agglutinating	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+
2	Anti-Pn Poly	2+	2+	+	+	+	$\pm$	$\pm$	—	—	—	—	—	—	—	—
3	Imm Chicken I	3+	2+	2+	2+	+	+	+	+	$\pm$	$\pm$	—	—	—	—	—
4	Imm Chicken III	+	+	+	$\pm$	$\pm$	$\pm$	—	—	—	—	—	—	—	—	—
5	Normal chicken	—	—	No other dilution run												
6	Pneusolin	—	—	No other dilution run												
7	Aged human	—	—	No other dilution run												

- 1 Agglutinating serum (diagnostic) from N Y State Board of Health
  - 2 Lederle's therapeutic serum, polyvalent
  - 3 Immunized chicken serum prepared by injecting 15 c c of heavy culture of pneumococcus, Type III, into peritoneal cavity, bled in eight days
  - 4 Immunized chicken serum prepared as above but with second injection of 20 c c in eight days, third injection of 10 c c in eight days and bled after nine days
  - 5 Normal aged chicken serum
  - 6 Mulford's pneumolin
  - 7 Aged normal human serum
- Readings taken after two hours in 37 C water bath and twelve hours in icebox

dilutions of 1 10 up to 1 12 and negative thereafter. Lederle's polyvalent antipneumococcic serum (commercial), which was 3 plus in dilutions of 1 1 and 1 2, 2 plus in a dilution of 1 3, plus in a dilution of 1 4 and negative thereafter, of the serum from a chicken injected intraperitoneally with 15 c c of a virulent Type 2 pneumococcus culture and bled eight days later, which was 4 plus in a dilution of 1 1, 3 plus in a dilution of 1 2, 2 plus in dilutions of 1 3 up to 1 6, plus in dilutions of 1 7 up to 1 9,  $\pm$  in a dilution of 1 10 and negative thereafter, of a chicken injected with 15 c c of virulent Type 2 pneumococcus culture intraperitoneally, a second injection of 25 c c of such a culture in eight days, and an equal injection of a similar culture seven days later, and bled fourteen days after the last injection, which was 2 plus in dilutions of 1 1 and 1 2, plus in dilutions of 1 3 up to 1 5,  $\pm$  in dilutions of 1 6 and 1 7 and minus thereafter, of normal chicken serum which showed no agglutination whatever, of pneumolin which showed no agglutination, of aged normal human serum which

again showed no agglutination. The readings were made after two hours in the water bath at 37 C and twelve hours in the icebox.

This experiment was made to determine the agglutinating power to the Type 3 pneumococcus of the diagnostic serum from the New York State Board of Health, which was 4 plus in dilutions up to 1:15, of Lederle (polyvalent) antipneumococcic serum which was 2 plus in dilutions of 1:1 and 1:2, plus in dilutions of 1:3 up to 1:5,  $\pm$  in dilutions of 1:6 and 1:7, and minus thereafter, of the serum from chickens which had been given an intraperitoneal injection of 15 c.c. of virulent Type 3 pneumococcus culture and bled eight days later, which was 3 plus in a dilution of 1:1, 2 plus in dilutions of 1:2 up to 1:4, plus in dilutions of 1:5 up to 1:8 and  $\pm$  in dilutions of 1:9 and 1:10 and minus thereafter, of the serum from chickens injected as those above, but with a second injection of 20 c.c. eight days after the first, and a third injection of 10 c.c. eight days later, and bled nine days after the last injection, which was plus in dilutions of 1:1 up to 1:3,  $\pm$  in dilutions of 1:4 up to 1:6 and minus thereafter, of normal chicken serum which showed no agglutination, of pneumolin which showed no agglutination and of aged normal human serum which showed no agglutination. These readings were made after two hours in a water bath at 37 C and twelve hours in the icebox.

The aged normal chicken serum, the aged normal human serum and pneumolin were shown to have no agglutinating power in the Types 2 and 3 pneumococcus where they were used. It was shown that agglutination can be produced in chicken serum by intraperitoneal injections of living cultures of pneumococcus. From this it will be seen that the protective substance against the pneumococcus found in normal chicken serum is not an agglutinin.

This experiment was performed to show the comparative protection to Type 3 pneumococcus of various serums. Table 4 A is the control sheet. No pneumococcus was given in the first group, but one mouse was injected intraperitoneally with 1 c.c. of aged normal human serum, a second with 1 c.c. of fresh normal human serum, a third with 1 c.c. of Lederle commercial antipneumococcic serum (polyvalent), a fourth with pneumolin 1 c.c., a fifth with aged normal human serum 1 c.c., a sixth with 1 c.c. of the serum from chickens that had received a large intraperitoneal injection of live culture of pneumococcus Type 3. All survived. In the second group no serum was given, but one mouse was given 0.1 c.c. of the peritoneal washings from a mouse previously chilled and injected with a virulent Type 3 pneumococcus intraperitoneally. The virulence was increased in the usual manner by chilling the animals and injecting from one to another until the death of control animals verified a highly virulent organism and a check proved it to be free from contamination. This mouse lived from thirty-one to forty hours,

TABLE 4—Comparative Protection to Type 3, *Pneumococcus*

Controls			Time, 12/29/23	Serum	A	Time, 12/29/23	Died	Hours	Postmortem Findings	Control:
W	None	4 p m	Aged N/human, 1 cc	A		10 a m	Survived	31-40 31-40 52-64	P P P	
R	None	4 p m	Fresh N/human, 1 cc			10 a m	Survived			
Bl	None	4 p m	Anti-Pn Poly 1 cc			10 a m	Survived			
Br	None	4 p m	Pneusolin, 1 cc			10 a m	Survived			
R + Bl	None	4 p m	Aged N/chicken, 1 cc			10 a m	Survived			
R + Br	None	4 p m	Immune chicken III, 1 cc			10 a m	Survived			
W	0 1 cc	4 p m	None	B		7 p m	11 a m 12/31/23	43 48 52-64	P P P	31-40 31-40 31-40
R	0 001 cc	4 p m	Aged N/human			7 p m	4 p m 12/31/23			
Bl	0 0001 cc	4 p m	Aged N/human			7 p m	8 p m to 8 a m, night of 31st			
Bl	0 00001 cc	4 p m	Aged N/human			7 p m	Survived			
Br	0 000001 cc	4 p m	Aged N/human			7 p m	Survived			
Br	0 0000001 cc	4 p m	Aged N/human			7 p m	Survived			
W	0 1 cc	4 p m	Fresh N/human	C		7 p m	11 p m to 8 a m, night of 30th	31-40 48 52-64 52-64	P P P P	31-40 31-40 31-40 52-64
R	0 001 cc	4 p m	Fresh N/human			7 p m	4 p m, 12/31/23			
Bl	0 0001 cc	4 p m	Fresh N/human			7 p m	Night of 31st			
Bl	0 00001 cc	4 p m	Fresh N/human			7 p m	Night of 31st			
Br	0 00001 cc	4 p m	Fresh N/human			7 p m	Survived			
Br	0 0000001 cc	4 p m	Fresh N/human			7 p m	Survived			
W	0 1 cc	4 p m	Anti Pn Poly (Lederle)	D		7 p m	11 p m to 8 a m, night of 30th	31-40 31-40 52-64 47 52-64	P P P P	31-40 31-40 52-64 52-64
R	0 001 cc	4 p m	Anti-Pn Poly (Lederle)			7 p m	Night of 31st			
Bl	0 00001 cc	4 p m	Anti-Pn Poly (Lederle)			7 p m	3 p m, 12/31/23			
Bl	0 00001 cc	4 p m	Anti-Pn Poly (Lederle)			7 p m	Night of 31st			
Br	0 0000001 cc	4 p m	Anti-Pn Poly (Lederle)			7 p m	Survived			
Br	0 0000001 cc	4 p m	Anti-Pn Poly (Lederle)			7 p m	Survived			
W	0 1 cc	4 p m	Pneusolin (Mulford)	D		7 p m	11 p m to 8 a m, night of 30th	31-40 52-64 31-40 42 45	P P P P	31-40 31-40 31-40 52-64 52-64
R	0 001 cc	4 p m	Pneusolin (Mulford)			7 p m	Night of 31st			
Bl	0 00001 cc	4 p m	Pneusolin (Mulford)			7 p m	10 a m, 12/31/23			
Bl	0 00001 cc	4 p m	Pneusolin (Mulford)			7 p m	1 p m, 12/31/23			
Br	0 0000001 cc	4 p m	Pneusolin (Mulford)			7 p m	Survived			
Br	0 0000001 cc	4 p m	Pneusolin (Mulford)			7 p m	Survived			
W	0 1 cc	4 p m	Normal aged chicken	D		7 p m	Night of 30th, 11 p m to 8 a m	31-40 10 52-64	P P P	31-40 31-40 31-40
R	0 001 cc	4 p m	Normal aged chicken			7 p m	8 30 a m, 12/31/23			
Bl	0 0001 cc	4 p m	Normal aged chicken			7 p m	Night of 31st, 8 p m to 8 a m			
Bl	0 00001 cc	4 p m	Normal aged chicken			7 p m	Survived			
Br	0 000001 cc	4 p m	Normal aged chicken			7 p m	Survived			
Br	0 0000001 cc	4 p m	Normal aged chicken			7 p m	Survived			
W	0 1 cc	4 p m	Immunized Chicken III	D		7 p m	Night of 30th, 11 p m to 8 a m	31-40 31-40 31-40 42	P P P P	31-40 31-40 31-40 52-64 52-64
R	0 001 cc	4 p m	Immunized Chicken III			7 p m	Night of 30th			
Bl	0 0001 cc	4 p m	Immunized Chicken III			7 p m	Night of 30th			
Bl	0 00001 cc	4 p m	Immunized Chicken III			7 p m	Night of 30th			
Br	0 000001 cc	4 p m	Immunized Chicken III			7 p m	10 a m, 12/31/23			
Br	0 0000001 cc	4 p m	Immunized Chicken III			7 p m	Survived			

and a necropsy culture made from the peritoneal cavity yielded a pure Type 3 pneumococcus. A second mouse was injected with 0.001 c.c. and died in thirty-one to forty hours. The culture showed a pure Type 3 pneumococcus. A third mouse was injected with 0.00001 c.c. and lived from fifty-two to sixty-four hours, this mouse also yielded a pure Type 3 pneumococcus on necropsy intraperitoneal culture. A fourth mouse was injected intraperitoneally with 0.0000001 c.c. and survived. These animals constituted our control for this set of tables.

In Table 4B is shown the protection of aged normal human serum to the Type 3 pneumococcus. The first mouse was given 0.1 c.c. of the Type 3 pneumococcal peritoneal washings, as before mentioned, and three hours later 1 c.c. of aged normal human serum intraperitoneally. This mouse lived for forty-three hours, the control animal with the same dosage living from thirty-one to forty hours. A pure Type 3 pneumococcus was recovered from the peritoneal cavity at necropsy. A second and third mouse were injected with 0.001 c.c. each of the peritoneal washings intraperitoneally, and three hours later were given 1 c.c. of aged normal human serum intraperitoneally, one living for forty-eight hours, the other from fifty-two to sixty-four hours, in contrast to the controls having the same dosage of pneumococcus, which lived from thirty-one to forty hours. A pure Type 3 pneumococcus was recovered from the peritoneal cavity at necropsy. A fourth and fifth mouse each received 0.00001 c.c. of the peritoneal washings and three hours later were given 1 c.c. of aged normal human serum each, both survived. A sixth and seventh mouse were each given 0.0000001 c.c. of the peritoneal washings and three hours later 1 c.c. of the aged normal human serum, both survived.

The next group is an exact duplication of the group just described, except that fresh normal human serum was used instead of aged normal human serum, the mouse having 0.1 c.c. of the peritoneal washings lived from thirty-one to forty hours, the control animal with the same dosage living the same number of hours. Of the two mice receiving 0.001 c.c. each of the peritoneal washings, one lived for forty-eight hours, the other from fifty-two to sixty-four hours, the control animal living from thirty-one to forty hours. Of the two mice receiving 0.00001 c.c. of the peritoneal washings, one lived from fifty-two to sixty-four hours (which was the same period of life as the control animal), the other survived. The two mice that were given 0.0000001 c.c. of the peritoneal washings both survived, as did the control. The mice that died all gave a pure Type 3 pneumococcus culture from the peritoneal cavity at necropsy.

The next group, Table 4C, is again an exact repetition, except that Lederle's polyvalent antipneumococcal serum replaced the human serum, the mouse receiving 0.1 c.c. of the peritoneal washings lived from thirty-one to forty hours, as did the control, of the two mice receiving 0.001

c c one lived from thirty-one to forty hours, the other from fifty-two to sixty-four hours, the control living from thirty-one to forty hours, of the two mice receiving 0 00001 c c, one lived for forty-seven hours, the other from fifty-two to sixty-four hours, the controls living from fifty-two to sixty-four hours, of the two mice receiving 0 0000001 c c both survived, as did the control. A pure Type 3 pneumococcus was recovered from the peritoneum on necropsy in all the mice that died.

In the next group, the same plan was again followed, but pneumolin was used in place of the antipneumococcic serum, the mouse receiving 0 1 c c of the peritoneal washings lived from thirty-one to forty hours, as did the control, of the two mice receiving 0 001 c c one lived from fifty-two to sixty-four hours, the other survived the control, living from thirty-one to forty hours, this survival we are at a loss to explain, since the mice with a higher dilution of the peritoneal washings than this died more promptly than did the control animals, of the mice receiving 0 00001 c c of the peritoneal washings, one lived forty-two and the other forty-five hours, the control living from fifty-two to sixty-four hours. The mice receiving higher dilutions of the peritoneal washings than this survived, as did the controls. The mice dying all yielded a pure Type 3 pneumococcus from the peritoneum at necropsy.

The next group, Table 4 D, is again a repetition of the foregoing, but using aged normal chicken serum as the protecting serum, the mouse receiving 0 1 c c of the peritoneal washings intraperitoneally lived from thirty-one to forty hours, as did the control, of the two mice receiving 0 001 c c of the peritoneal washings, one lived forty hours, the other from fifty-two to sixty-four hours, the control living from thirty-one to forty hours. The mice receiving 0 00001 c c or higher dilutions of the peritoneal washings all survived. Those mice dying all yielded a pure Type 3 pneumococcus from the peritoneum at necropsy. In the next group, serum from a chicken having had intraperitoneal injections of a pneumococcus culture as described in the observations of the control sheet, was used as the protective serum. The mouse receiving 0 1 c c of the peritoneal washings lived from thirty-one to forty hours, as did the control, of the mice receiving 0 001 c c of the peritoneal washings, both lived from thirty-one to forty hours, as did the control, of the mice receiving 0 00001 c c of the peritoneal washings, one lived from thirty-one to forty hours, the other forty-two hours, the control living from fifty-two to sixty-four hours. The mice receiving 0 0000001 c c of the peritoneal washings both survived. A pure Type 3 pneumococcus was recovered from the peritoneum at necropsy.

It will be seen that the aged normal human serum and the aged normal chicken serum are the only ones of the group offering any considerable degree of protection. In each case the mice survived, the controls having an equal dose of the same pneumococcic peritoneal

TABLE 5—Control Sheet

## A

Controls	Pn II	Time, 2/25/24	Serum	Time, 2/25/24	Died	Hours	Post- mortem Culture
W	None		Aged N/human, 1 cc		Survived		
R	None		Fresh N/human, 1 cc		Survived		
Bi	None		Anti-Pn Poly, 1 cc		Survived		
Br	None		Phenol, 1 cc		Survived		
R + B	None		Aged N/chicken, 1 cc		Survived		
R + Br	None		Immune chicken, 1 cc		Survived		
W	0.1 cc	3 p m	None		5 p m, 2/26/24	26	P
R	0.001 cc	3 p m	None		9 p m, 2/26/24	30	P
Bi	0.0001 cc	3 p m	None		3 p m, 2/27/24	48	P
Br	0.000001 cc	3 p m	None		Night of 26th	90-40	P
					3 p m, 2/27/24	48	P
					6 p m, 2/27/24	51	P
					Night of 27th	54-62	P
					Night of 27th	54-62	P

## B

W	0.1 cc	3 p m	Aged N/human, 1 cc		Night of 25th	16-18	Pure Pn II
W	0.1 cc	3 p m	Aged N/human, 1 cc		2/25/24, 5 p m	26	P
R	0.001 cc	3 p m	Aged N/human, 1 cc		Night of 26th	30-42	P
R	0.001 cc	3 p m	Aged N/human, 1 cc		2/27/24, 8 p m	53	P
Bi	0.0001 cc	3 p m	Aged N/human, 1 cc		Night of 27th	53-65	P
Bi	0.0001 cc	3 p m	Aged N/human, 1 cc		Survived		
Br	0.000001 cc	3 p m	Aged N/human, 1 cc		Survived		
Br	0.000001 cc	3 p m	Aged N/human, 1 cc		Survived		
W	0.1 cc	3 p m	Fresh N/human, 1 cc		2/26/24, 11 a m	20	P
W	0.1 cc	3 p m	Fresh N/human, 1 cc		2/26/24, 12 30 p m	22	P
R	0.001 cc	3 p m	Fresh N/human, 1 cc		Night of 26th	30-42	P
R	0.001 cc	3 p m	Fresh N/human, 1 cc		Night of 26th	53-65	P
Bi	0.00001 cc	3 p m	Fresh N/human, 1 cc		Night of 27th	53-65	P
Bi	0.00001 cc	3 p m	Fresh N/human, 1 cc		Survived		
Br	0.000001 cc	3 p m	Fresh N/human, 1 cc		Survived		
Br	0.000001 cc	3 p m	Fresh N/human, 1 cc		Survived		

## C

W	0.1 cc	3 p m	Anti Pn Poly, 1 cc		2/26/24, 2 30 p m	24	P
W	0.1 cc	3 p m	Anti Pn Poly, 1 cc		2/26/24, 5 p m	26	P
R	0.001 cc	3 p m	Anti Pn Poly, 1 cc		2/26/24, 9 p m	30	P
R	0.001 cc	3 p m	Anti Pn Poly, 1 cc		Night of 26th	30-40	P
Bi	0.00001 cc	3 p m	Anti Pn Poly, 1 cc		Survived		
Bi	0.00001 cc	3 p m	Anti Pn Poly, 1 cc		Survived		
Br	0.000001 cc	3 p m	Anti Pn Poly, 1 cc		Survived		
Br	0.000001 cc	3 p m	Anti Pn Poly, 1 cc		Survived		

W	0 1 c c	3 p m	Pneusolin, 1 c c	7 p m	2/26/24, 2 30 p m	24	P
W	0 1 c c	3 p m	Pneusolin, 1 c c	7 p m	2/26/24, 9 p m	30	P
R	0 001 c c	3 p m	Pneusolin, 1 c c	7 p m	2/26/24, 6 p m	27	P
R	0 001 c c	3 p m	Pneusolin, 1 c c	7 p m	Night of 26th	30 10	P
Bl	0 00001 c c	3 p m	Pneusolin, 1 c c	7 p m	Survived		
Bl	0 00001 c c	3 p m	Pneusolin, 1 c c	7 p m	Survived		
Br	0 0000001 c c	3 p m	Pneusolin, 1 c c	7 p m	Survived		
Br	0 0000001 c c	3 p m	Pneusolin, 1 c c	7 p m	Survived		
D							
W	0 1 c c	3 p m	Aged N/chicken, 1 c c	7 p m	2/26/24, 3 p m	24	P
W	0 1 c c	3 p m	Aged N/chicken, 1 c c	7 p m	Night of 26th	30-10	P
R	0 001 c c	3 p m	Aged N/chicken, 1 c c	7 p m	2/26/24, 9 p m	30	P
R	0 001 c c	3 p m	Aged N/chicken, 1 c c	7 p m	Night of 26th	30 10	P
Bl	0 00001 c c	3 p m	Aged N/chicken, 1 c c	7 p m	2/27/23, 6 p m	51	P
Bl	0 00001 c c	3 p m	Aged N/chicken, 1 c c	7 p m	Survived		
Br	0 0000001 c c	3 p m	Aged N/chicken, 1 c c	7 p m	Survived		
Br	0 0000001 c c	3 p m	Aged N/chicken, 1 c c	7 p m	Survived		
W	0 1 c c	3 p m	Immun Ohlek II, 1 c c	7 p m	2/26/24, 11 a m	20	P
W	0 1 c c	3 p m	Immun Ohlek II, 1 c c	7 p m	2/26/24, 2 30 p m	21	P
R	0 001 c c	3 p m	Immun Ohlek II, 1 c c	7 p m	Night of 26th	30-10	P
R	0 001 c c	3 p m	Immun Ohlek II, 1 c c	7 p m	Survived		
Bl	0 00001 c c	3 p m	Immun Ohlek II, 1 c c	7 p m	Night of 26th	30 10	P
Bl	0 00001 c c	3 p m	Immun Ohlek II, 1 c c	7 p m	Survived		
Br	0 0000001 c c	3 p m	Immun Ohlek II, 1 c c	7 p m	Survived		
Br	0 0000001 c c	3 p m	Immun Ohlek II, 1 c c	7 p m	Survived		
E							
W	0 1 c c	3/17/24	None		3/18/24, 4 p m	20	Pure Pn
W	0 1 c c	8 p m	None		Night of 18th	21 36	P
R	0 001 c c	8 p m	None		Night of 18th	24 36	P
R	0 001 c c	8 p m	None		11 a m, 3/19/24	39	P
Bl	0 00001 c c	8 p m	None		6 p m, 3/19/24	46	P
Bl	0 00001 c c	8 p m	None		Survived		
Br	0 0000001 c c	8 p m	None		Night of 20th	72 84	Sinear neg
Br	0 0000001 c c	8 p m	None		Survived		
F							
W	0 1 c c	8 p m	N/chicken, 1 c c (72 hr old)	3/17/24	Survived		
W	0 1 c c	8 p m	N/chicken, 1 c c (72 hr old)	12 midnight	Survived		
R	0 001 c c	8 p m	N/chicken, 1 c c (72 hr old)	12 midnight	Survived		
R	0 001 c c	8 p m	N/chicken, 1 c c (72 hr old)	12 midnight	Survived		
Bl	0 00001 c c	8 p m	N/chicken, 1 c c (72 hr old)	12 midnight	Survived		
Bl	0 00001 c c	8 p m	N/chicken, 1 c c (72 hr old)	12 midnight	Survived		
Br	0 0000001 c c	8 p m	N/chicken, 1 c c (72 hr old)	12 midnight	Survived		
Br	0 0000001 c c	8 p m	N/chicken, 1 c c (72 hr old)	12 midnight	Survived		
	None	8 p m	N/chicken, 1 c c (72 hr old)	12 midnight	Survived		

N/chicken serum used was very old and attenuated



washings without serum died in from fifty-two to sixty-four hours, those having the next higher dose, that is, 0.001 c c, showed a slightly prolonged period of life. In the group having the fresh human serum, there is one survival more than in the control, but with no prolongation of life above the controls in the other animals. Had the normal chicken serum used been fresher, a much more striking result might have been expected, as shown in another group of experiments, that used here was unpreserved and although sterile, had been produced about four months previously.

In the fifteenth series of experiments, precisely the same work was done as in the fourteenth series, but replacing the Type 3 pneumococcus with a Type 2, which, in our hands, developed a higher degree of virulence than did either of the other two groups.

Table 5 A is our control sheet. Each of the mice in the first group receiving 1 c c in each case of the various serums used, but having no pneumococcal injection, survived, of the controls in which no serum was given, but only intraperitoneal injections of the highly virulent peritoneal washings recovered from a mouse previously injected with the Type 2 pneumococcus, the two receiving 0.1 c c lived for twenty-six and thirty hours, respectively, of the two receiving 0.001 c c, one lived for forty-eight hours, the other from thirty to forty hours, of the two receiving 0.00001 c c, one lived for forty-eight hours, the other for fifty-one hours. The two receiving 0.0000001 c c both lived from fifty-four to sixty-two hours. A pure Type 2 pneumococcus was recovered from the peritoneum at necropsy in every case.

In Group 1 B (Table 5), each mouse received 1 c c of aged normal human serum four hours after the intraperitoneal injection of the same peritoneal washings employed in the control animal. Of those receiving 0.1 c c of the peritoneal washings, one lived from sixteen to eighteen hours, the other for twenty-six hours, in contrast to the controls having the same dosage which lived for twenty-six and thirty hours, respectively, of the two receiving 0.001 c c each, one lived from thirty to forty-two hours, the other fifty-three hours, in contrast to the controls which lived for forty-eight and from thirty to forty hours, respectively. Of those receiving 0.00001 c c each, one lived from fifty-three to sixty-five hours, the other survived, in contrast to the controls which lived for forty-eight and fifty-one hours. The two receiving 0.0000001 c c each both survived. A pure Type 2 pneumococcus was recovered at necropsy in all the animals that died.

In Group 2 B, fresh normal human serum in quantities of 1 c c to each mouse replaced the aged normal human serum used in the foregoing group four hours after the injection of the Type 2 peritoneal washings. Of the two mice receiving 0.1 c c of the peritoneal washings, one lived for twenty hours and the other for twenty-two hours, in contrast to the controls which lived for twenty-six

and thirty hours, respectively. Of the two receiving 0.001 c.c., one lived from thirty to forty-two hours, the other from fifty-three to sixty-five hours, in contrast to the controls which lived for forty-eight hours and from thirty to forty hours. Of the two receiving 0.00001 c.c., one lived from fifty-three to sixty-five hours, the other survived, in contrast to the controls which lived for forty-eight and fifty-one hours, respectively. The two receiving 0.0000001 c.c. both survived. In every case, pure Type 2 pneumococcus was recovered from the peritoneum at necropsy.

Group 1 C is a repetition of the foregoing group, but replacing the human serum with Lederle's polyvalent antipneumococcic serum, 1 c.c. to each mouse, four hours after the intraperitoneal injection of the pneumococcic peritoneal washings. Of the two mice receiving 0.1 c.c. of the peritoneal washings intraperitoneally, one lived for twenty-four hours and the other for twenty-six hours, in contrast to the controls, which lived for twenty-six and thirty hours, respectively. Of the two receiving 0.001 c.c., one lived for thirty hours and the other from thirty to forty hours, in contrast to the controls, which lived for forty-eight and from thirty to forty hours. The two mice receiving 0.00001 c.c. each of the peritoneal washings and the two receiving 0.0000001 c.c. each survived. In every case a pure Type 2 pneumococcus was recovered from the peritoneum when the mice died.

In Group 2 C, 1 c.c. of pneumolin was given each mouse intraperitoneally four hours after the injection of the pneumococcic peritoneal washings had been given intraperitoneally. Of the two mice given 0.1 c.c. of the peritoneal washings, one lived for twenty-four hours, the other for thirty hours. The controls lived for twenty-six and thirty hours, respectively. Of the two mice receiving 0.001 c.c., one lived for twenty-seven hours, the other from thirty to forty hours, in contrast to the controls which lived for forty-eight and from thirty to forty hours. The two mice receiving 0.00001 c.c. and those receiving 0.0000001 c.c. of the peritoneal washings all survived. A pure Type 2 pneumococcus culture was recovered from the peritoneum of those mice that died.

In Group 1 D, 1 c.c. of aged normal chicken serum was given intraperitoneally to each mouse four hours after intraperitoneal injection of the Type 2 pneumococcic peritoneal washings. Of the two mice receiving 0.1 c.c. of the peritoneal washings, one lived for twenty-four hours, the other from thirty to forty hours. The controls with the same dosage of the same peritoneal washings lived for twenty-six and thirty hours. The two mice that were given 0.001 c.c. of the peritoneal washings lived for thirty hours and from thirty to forty hours, the controls lived for forty-eight hours and from thirty to forty hours. Of the two that were given 0.00001 c.c., one lived for fifty-one hours, the other survived. The controls lived for forty-eight and fifty-one hours. The two that

were given 0 0000001 c c of the peritoneal washings both survived A pure Type 2 pneumococcus was recovered at necropsy in all the mice that died

In Group 2 D, the protective serum used was from chickens which had received large doses of Type 2 pneumococcus intraperitoneally and were bled nine days later One cubic centimeter was given intraperitoneally to each mouse four hours after the injection of the Type 2 pneumococcus peritoneal washings Of the two mice in which 0 1 c c. of the peritoneal washings were given intraperitoneally, one lived for twenty hours, the other for twenty-four hours The controls lived for twenty-six and thirty hours Of the two mice receiving 0 001 c c, one lived from thirty to forty hours, and the other survived We are unable to explain this survival The control mice lived for forty-eight hours and from thirty to forty hours, respectively Of the two mice receiving 0 00001 c c of the peritoneal washings, one lived from thirty to forty hours and the other survived The controls lived for forty-eight and fifty-one hours The two mice receiving 0 0000001 c c each both survived A pure Type 2 pneumococcus was recovered from the peritoneum at necropsy

From our previous experience we were led to expect a very much higher degree of protection from normal chicken serum than was shown in this group of experiments, and set about to investigate this point We found that the aged normal chicken serum that was used was unpreserved and had been produced between six and seven months previously. We are, however, including the findings in this report because we feel that it is valuable to show what may be expected from very old serum when unpreserved, even if kept in a sterile condition To check this point, a fresh normal chicken serum was prepared and was used when seventy-two hours old in Table 5 E

In E, a high virulence was again developed in our Type 2 pneumococcus, and as controls two mice were injected with 0 1 c c each of the peritoneal washings of this organism intraperitoneally, one lived for twenty hours, the other from twenty-four to thirty-six hours, and a pure Type 2 pneumococcus was recovered from the peritoneum at necropsy Two others were each injected with 0 001 c c of the peritoneal washings intraperitoneally and lived from twenty-four to thirty-six and thirty-nine hours A pure Type 2 pneumococcus was recovered from the peritoneum at necropsy Two others were injected with 0 00001 c c each of the same peritoneal washings, one lived for forty-six hours and the other survived A pure Type 2 pneumococcus was recovered from the peritoneum of the mouse that died Two others were injected with 0 0000001 c c each of the peritoneal washings, one survived, the other died in from seventy-two to eighty-four hours However, necropsy of the peritoneal cavity disclosed a contamination in the mouse that died, hence no conclusions can be drawn

In Group 2 E, two mice each with a dosage of the same peritoneal washings as used in the foregoing, were injected intraperitoneally, that is, two receiving 0.1 c.c. each, two receiving 0.001 c.c. each, two receiving 0.00001 c.c. each and two receiving 0.0000001 c.c. each intraperitoneally. Each mouse was given 1 c.c. of normal chicken serum seventy-two hours old, four hours after the intraperitoneal injection of the Type 2 pneumococcal peritoneal washings, all survived. A control mouse receiving no pneumococcal injection, but 1 c.c. of this same normal chicken serum, survived.

In the fifteenth series, all of the serums used apparently gave some protection. The normal chicken serum used when seventy-two hours old gave complete protection to the same dosage of the Type 2 pneumococcus, which killed the control animals receiving 0.1 c.c. of the injection in twenty hours and from twenty-four to thirty-six hours. Pneusolin and Lederle's polyvalent antipneumococcal serum each gave protection to a dosage as high as 0.00001 c.c. The control animals having this same dosage of the same peritoneal washings lived for forty-eight and fifty-one hours. The protection afforded by other serums used is negligible.

Our results, clinically, with children, seem to indicate that the period elapsing between the time of infection and the time when serum was administered, and also the dosage of the serum given were factors in the end-results obtained. To determine this point, Experiments 6, 7 and 8 were carried out.

In Table 6, the peritoneal washings from a mouse previously injected with a virulent Type 2 pneumococcus were given intraperitoneally, 0.0001 c.c. to each of two mice, one lived for forty-seven hours, the other for forty-nine hours. A pure Type 3 pneumococcus was recovered at necropsy from the peritoneum in each case. Twelve other mice were each given 0.00001 c.c. intraperitoneally of the same peritoneal washings, three of these were immediately given intraperitoneally 0.5 c.c., 0.75 c.c. and 1 c.c. of normal chicken serum, respectively. The mouse receiving 1 c.c. of the chicken serum lived for ninety-six hours, no necropsy was possible, the other two mice survived. Three hours after the intraperitoneal injection of the peritoneal washings, three other mice were given 0.5 c.c., 0.75 c.c. and 1 c.c., respectively, of the normal chicken serum intraperitoneally, all survived. Six hours after the intraperitoneal injection of the peritoneal washings, another group of three mice was given 0.5 c.c., 0.75 c.c. and 1 c.c. of the normal chicken serum, intraperitoneally. The one receiving 0.5 c.c. chicken serum lived for ninety-six hours and no necropsy was possible. The other two mice survived. Eight hours after the injection of the peritoneal washings a fourth group of three mice was given 0.5 c.c., 0.75 c.c. and 1 c.c. of the normal chicken serum, respectively. The one receiving 0.5 c.c. survived, the one receiving 0.75 c.c. died in ninety-six hours, no necropsy was possible, the one receiving 1 c.c. of normal chicken serum

died in seventy-two hours and a pure Type 3 pneumococcus was recovered from the peritoneum at necropsy. A control mouse was given 1 c c of the same chicken serum intraperitoneally, but with no peritoneal washings, and survived.

In Table 7, one mouse, as a control, was given 1 c c intraperitoneally of the aged normal chicken serum used in this experiment and survived. Twenty-five other mice were each given 0.001 c c of the peritoneal washings from a mouse previously injected with a virulent Type 2 pneumococcus. One of these received no chicken serum and died in from twelve to eighteen hours. Another mouse receiving 0.00001 c c of the same peritoneal washings and no chicken serum died in forty-six hours. A pure Type 2 pneumococcus was recovered from the peri-

TABLE 6—*Peritoneal Washings from a Mouse*

		Pn III	Time, 10/15/23	Chicken Serum	Time, 10/15/23	Died	Hours	Condi- tion
Control		0.00001 c c	2 p m	1.0 c c	2 p m	Survived		
Control		0.00001 c c	2 p m			1 p m, 10/17/23	47	P
Control		0.00001 c c	2 p m			3 p m, 10/17/23	49	P
Simult	W	0.00001 c c	2 p m	0.5 c c	2 p m	Survived		
	R	0.00001 c c	2 p m	0.75 c c	2 p m	Survived		
	B	0.00001 c c	2 p m	1.00 c c	2 p m	Night of 10/19/23	96	Not ex- amined
3 hr	W	0.00001 c c	2 p m	0.5 c c	5 p m	Survived		
	R	0.00001 c c	2 p m	0.75 c c	5 p m	Survived		
	B	0.00001 c c	2 p m	1.00 c c	5 p m	Survived		
6 hr	W	0.00001 c c	2 p m	0.5 c c	8 p m	Night of 10/19/23	96	Not ex- amined
	R	0.00001 c c	2 p m	0.75 c c	8 p m	Survived		
	B	0.00001 c c	2 p m	1.00 c c	8 p m	Survived		
8 hr	W	0.00001 c c	2 p m	0.5 c c	10 p m	Survived		
	R	0.00001 c c	2 p m	0.75 c c	10 p m	Night of 10/19/23	96	Not ex- amined
	B	0.00001 c c	2 p m	1.00 c c	10 p m	Night of 10/18/23	72	P

P denotes pure pneumococcus recovered from peritoneal cavity postmortem.

toneum of each at necropsy. Six other mice were given an intraperitoneal injection of normal chicken serum simultaneously with the injection of the peritoneal washings. Two of these were given 0.5 c c of the normal chicken serum, one living from fifty-six to sixty-four hours, in contrast to the control which lived from twelve to eighteen hours, the other survived. A pure Type 2 pneumococcus culture was recovered from the peritoneum of the mouse that died. Of two others receiving 0.75 c c of the normal chicken serum, one lived for forty-nine hours and yielded a pure culture of Type 2 pneumococcus at necropsy, the other survived. Of the other two mice receiving 1 c c of normal chicken serum intraperitoneally, one showed a contamination at necropsy culture from the peritoneum, the other survived. Three hours after the intraperitoneal injection of the peritoneal washings, two mice were given 0.5 c c of normal chicken serum intraperitoneally, one living from thirty-six to forty-four hours, in contrast to the control which

lived from twelve to eighteen hours and yielded a pure Type 2 pneumococcus culture from the peritoneum at necropsy. The other showed a contamination. Of two other mice having 0.75 c.c. of normal chicken serum intraperitoneally, one lived for fifty-one hours, the other for fifty hours and from each a pure Type 2 pneumococcus culture was obtained at necropsy. The other two mice were given 1 c.c. of normal chicken serum intraperitoneally and lived for fifty-two and forty-six hours, yielding a pure Type 2 pneumococcus culture from the peritoneum at necropsy. Six hours after the injection of the peritoneal washings, six other mice were given intraperitoneal injections of normal

TABLE 7—*Mouse as Control Given Serum*

		Pn II	Time, 11/18/23	N/Chick Serum	Time 11/18/23	Died	Hours	Condi- tion
Control	W	None		1.00 c.c.	12 m	Survived		
Control	R	0.001 c.c.	12 m	None		Night of 11/18/23	12-18	P
Control	B	0.0001 c.c.	12 m	None		10 a.m., 11/20/23	46	P
Simult	W	0.001 c.c.	12 m	0.5 c.c.	12 m	Night of 11/20/23	56-64	P
	R	0.001 c.c.	12 m	0.75 c.c.	12 m	Survived 1 p.m., 11/20/23	49	P
	B	0.001 c.c.	12 m	1.00 c.c.	12 m	Survived Survived		
3 hr	W	0.001 c.c.	12 m	0.5 c.c.	3 p.m.	Night of 11/19/23	36-44	P
	R	0.001 c.c.	12 m	0.75 c.c.	3 p.m.	3 p.m., 11/20/23	51	P
						2:30 p.m., 11/20/23	50	P
	B	0.001 c.c.	12 m	1.00 c.c.	3 p.m.	4 p.m., 11/20/23	52	P
						10 a.m., 11/20/23	46	P
6 hr	W	0.001 c.c.	12 m	0.5 c.c.	6 p.m.	6 p.m., 11/19/23	30	P
						8:30 a.m., 11/19/23	20	P
	R	0.001 c.c.	12 m	0.75 c.c.	6 p.m.	6 p.m., 11/19/23	30	P
						9:30 a.m., 11/19/23	22	P
	B	0.001 c.c.	12 m	1.00 c.c.	6 p.m.	9 p.m., 11/19/23	33	P
						8 a.m., 11/20/23	44	P
8 hr	W	0.001 c.c.	12 m	0.5 c.c.	8 p.m.	12:30 p.m., 11/19/23	24	P
						4 p.m., 11/19/23	28	P
	R	0.001 c.c.	12 m	0.75 c.c.	8 p.m.	10:30 a.m., 11/19/23	22	P
						8 a.m., 11/19/23	20	P
	B	0.001 c.c.	12 m	1.00 c.c.	8 p.m.	2:30 p.m., 11/19/23	27	P
						6 p.m., 11/19/23	30	P

N/chicken serum attenuated through age

P denotes pure pneumococcus recovered from peritoneal cavity postmortem

chicken serum, two receiving 0.5 c.c. lived for thirty and twenty hours, respectively, two receiving 0.75 c.c. lived for thirty and twenty-two hours, respectively, two receiving 1 c.c. lived for thirty-three and forty-four hours, respectively. A pure Type 2 pneumococcus culture was recovered from the peritoneum at necropsy from each of these six mice. Eight hours after the injection of the peritoneal washings, six other mice were given intraperitoneal injections of the normal chicken serum, two were given 0.5 c.c. each, and lived for twenty-four and twenty-eight hours, two others were given 0.75 c.c. each and lived for twenty-two and twenty hours, two others were given 1 c.c. each and lived for twenty-seven and thirty hours, respectively. A pure Type 2 pneumococcus culture was recovered from the peritoneum at necropsy in each of these six mice.

In Table 8, one mouse was given 1 c c of the normal chicken serum used in this experiment intraperitoneally and survived. Thirteen other mice were each given 0.001 c c of the peritoneal washings of a mouse that had previously been injected intraperitoneally with a virulent Type 1 pneumococcus. One of these was given no chicken serum and died in thirty-three hours, another mouse was given 0.00001 c c of the same peritoneal washings and no chicken serum and died in from thirty-three to forty-four hours. A pure Type 1 pneumococcus culture was recovered from the peritoneum of each at necropsy. Three other mice were given 0.5 c c, 0.75 c c and 1 c c, respectively, of aged normal chicken serum at the same time that the injection of the peritoneal washings were made, all survived. Three hours after the injection of the peritoneal washings, three other mice were given 0.5 c c, 0.75 c c

TABLE 8—*Mouse as Control Given Serum*

		Pn I	Time, 11/18/23	N/Chick Serum	Time 11/18/23	Died	Hours	Condi- tion
Control	W	None		1.00 c c	12 m	Survived		
Control	R	0.001 c c	12 m	None		9 p m, 11/19/23	33	P
Control	B	0.00001 c c	12 m	None		Night of 11/19/23	33-44	P
Simult	W	0.001 c c	12 m	0.5 c c	12 m	Survived		
	R	0.001 c c	12 m	0.75 c c	12 m	Survived		
	B	0.001 c c	12 m	1.00 c c	12 m	Survived		
3 hr	W	0.001 c c	12 m	0.5 c c	3 p m	Survived		
	R	0.001 c c	12 m	0.75 c c	3 p m	Survived		
	B	0.001 c c	12 m	1.00 c c	3 p m	Survived		
6 hr	W	0.001 c c	12 m	0.5 c c	6 p m	Survived		
	R	0.001 c c	12 m	0.75 c c	6 p m	Survived		
	B	0.001 c c	12 m	1.00 c c	6 p m	10:30 a m, 11/20/23	47	P
8 hr	W	0.001 c c	12 m	0.5 c c	8 p m	4 p m, 11/20/23	52	P
	R	0.001 c c	12 m	0.75 c c	8 p m	Night of 11/20/23	56-64	P
	B	0.001 c c	12 m	1.00 c c	8 p m	8:40 a m, 11/20/23	45	P

Type 1 pneumococcus used

P denotes pure pneumococcus recovered from peritoneal cavity postmortem

and 1 c c, respectively, of normal chicken serum intraperitoneally, all survived. Six hours after the intraperitoneal injections of the peritoneal washings, three other mice were given 0.5 c c, 0.75 c c and 1 c c, respectively, of the aged normal chicken serum intraperitoneally. The mouse receiving 1 c c lived for forty-seven hours and a pure Type 1 pneumococcus culture was recovered from the peritoneal cavity at necropsy. Eight hours after the injection of the intraperitoneal washings, the other three mice were given 0.5 c c, 0.75 c c and 1 c c, respectively, of the aged normal chicken serum intraperitoneally. The one receiving 0.5 c c lived for fifty-two hours, the one receiving 0.75 c c lived from fifty-six to sixty-four hours, the one receiving 1 c c lived for forty-five hours. From each of the three a pure Type 1 pneumococcus was recovered from the peritoneum at necropsy.

While the results in Experiments 6, 7 and 8 run quite parallel, Table 7 illustrates the points to be gathered perhaps more clearly at a glance than do the other two. We are here dealing with an organism

which, in a definite dosage, namely, 0.001 c c of the peritoneal washings of a mouse previously injected intraperitoneally with a Type 2 pneumococcus, killed a mouse in from twelve to eighteen hours. The six mice receiving this same dosage and simultaneously aged normal chicken serum intraperitoneally showed a considerable degree of protection. Had the organism been slightly less virulent or the chicken serum more fresh, this protection might have been complete. Each succeeding group receiving the chicken serum, that is, three hours, six hours and eight hours after inoculation, showed a shorter and shorter duration of life as the interval lengthened between the time of inoculation and administration of serum. The size of the dose of chicken serum seems to have made little difference in this experiment, this may have been due to either one of two factors: first, the mechanical irritation of so large a quantity as 1 c c in contrast to a smaller dosage, or that the smaller dosage gave all the available protection that was to be had.

The opsonic index was unsuccessfully attempted several times, the results were what one might expect from such an organism as the pneumococcus.

#### CONCLUSIONS

We conclude from these findings

- 1 That in the normal chicken serum a protective substance against the pneumococcus of Types 1, 2 and 3 is present
- 2 That this protective substance is not an agglutinin
- 3 That agglutinating power can be produced in the blood serum of chickens by the intraperitoneal injections of live pneumococci, but without increasing the protecting power of this serum
- 4 That the chicken is tolerant to large doses of pneumococci intraperitoneally, with no untoward results
- 5 That the protection afforded by chicken serum is inversely proportional to the period of time elapsing between the infection and the administration of the serum
- 6 That the protective power of chicken serum, if unpreserved, in time becomes very much attenuated even if kept under sterile conditions, and may finally become entirely inert
- 7 That the protection afforded by normal chicken serum is shared if at all, to a very much lesser degree by the other serums employed in these experiments

#### CLINICAL RESULTS

In the following report of our clinical results, our patients were all children in the wards of the Children's Mercy Hospital. A complete survey was made of all pneumonia patients in the hospital during the period included, regardless of the service they were on or whether or not they had been given chicken blood or serum. No selection of cases



TABLE 9—The Use of Chicken Blood and Serum in the Treatment of Pneumonia in Children

No	Age	Duration of Pneumonia Before Treatment	Lobar or Broncho	Roentgen Ray Posi- tive or Negative	Initial Reaction Before Blood or Serum			Blood or Serum Given			Normal in Days after Blood or Serum			Complications	
					Temp	Pulse	Resp	Amount	Type of Injection	Date	Temp	Pulse	Resp		
1	26 mo	No history 12 days after admission	Lobar	+	103.4	136	35	55 cc 95 cc	Intramuscular Intramuscular	10/25/22 10/27/22	Blood Blood	1	1	1	Diagnosis gastro enteritis and otitis media
2	1 yr	No history	Broncho as complicat if present		103	120	48	60 cc	Intramuscular	11/26/22	Blood	Died			
3	19 mo	24 hr before treatment	Broncho	+	105.8	160	50	250 cc 108 cc 247 cc	Intramuscular Intramuscular Intramuscular	11/27/22 11/29/22 11/27/22	Blood Blood Blood	8	8	8	Abscess from unabsorbed blood
4	2 yr	1 day before Px	Broncho	+	103	160	80	85 cc 267 cc	Intramuscular Intramuscular	12/2/22 11/8/22	Blood Blood	2	2	2	
5	12 mo	No history	Broncho	+	103	143	50	198 cc 193 cc	Intramuscular Intramuscular	11/10/22 11/18/22	Blood Blood	2	2	1	Abscess from blood
6	3 yr	No history	Broncho	+	103.6	140	40	195 cc 110 cc	Intramuscular Intramuscular	11/19/22 12/2/22	Blood Blood	1	1	1	
7	20 mo	No history	Broncho	H L D H C B J G M	102	138	42	205 cc 274 cc 290 cc	Intramuscular Intramuscular Intramuscular	12/2/22 12/2/22 1/11/23	Blood Blood Blood	2	1	1	
8	1 yr	5 days	Broncho	—	104.4	125	35	180 cc	Intramuscular	1/5/23	Blood	1	1	1	Temp normal after second injection
9	2 yr	No history	Lobar	+	102	140	35	230 cc 200 cc	Intramuscular Intramuscular	1/11/23 12/21/22	Blood Blood	1	3	1	
10	8 yr	No history	Lobar	+	103.5	130	45	145 cc	Intramuscular	12/22/22	Blood	2	2	2	Abscess from blood
11	8 yr	5 days	Lobar	+	104	115	35	230 cc 176 cc	Intramuscular Intramuscular	1/6/23 12/19/22	Blood Blood	1	1	1	
12	3 yr	4 days	Broncho	+	103	130	40	240 cc	Intramuscular	12/21/22	Blood	1	2	2	Abscess from blood 1/5/23
13	8 mo	No history	Lobar	Necropsy positive	104	135	48	100 cc	Intramuscular	12/20/22	Blood				
14	2 yr	No history	Lobar	+	104.2	150	40	113 cc 90 cc	Intramuscular Intramuscular	11/2/22 11/3/22	Blood Blood	11/5/22	11/11/22	11/5/22	Abscess from blood Empyema
15	4 yr	No history	Lobar	+	106	150	48	300 cc	Intramuscular	11/9/22	Blood	3	3	3	
16	9 yr	No history	Lobar	+	105	130	35	350 cc	Intramuscular	2/5/23 2/1/23	Serum Serum	2/8/23	2/8/23	2/8/23	Menigitis Died
17	9 mo	2 days	Lobar	+	104	130	42	200 cc 250 cc	Intramuscular Intramuscular	2/4/23 2/17/23	Serum Serum	Did not reach normal	Did not reach normal		
18	3 mo	2 days	Broncho	+	102.8	160	70	200 cc	Intramuscular	2/20/23	Serum	2	3	2	Erythema multiforme
19	12 mo	5 days	Lobar	+	103	140	40	300 cc	Intramuscular	2/24/23	Serum	2	3	2	
20	1 yr	2 days	Broncho	+	103	140	42	75 cc	Intramuscular	1/11/23	Blood	2	1	4	
21	2 mo	No history	Lobar	+	104.5	150	Not taken	250 cc 300 cc	Intramuscular Intramuscular	2/3/23 1/30/23	Serum Serum	5	Late	4	
22	No record	2 days	Lobar	+	104.5	150	48	200 cc	Intravenous	2/19/23	Serum	11	11	11	Endocarditis
23	8 yr	5 days	Lobar	+	105.2	145	45	300 cc	None given	None given		4	6	6	
24	4 days	4 days	Broncho	+	102.4	144	30	100 cc	Intravenous	3/3/23	Serum	2	2	1	
25	2 yr	No history	Lobar	+	102	120	35	200 cc	Intravenous	5/16/23	Serum	1	3	1	
26	5 yr	Indefinite	Lobar	+	104	130	37	80 cc	Intramuscular	6/15/23	Serum	1	3	1	
27	6 yr	24 hours	Lobar	+	103.8	130	38	200 cc	Intramuscular	6/15/23	Serum				

28	5 mo	No history	Broncho	+	102	120	35	150 cc	Intravenous	None given	9	11	9	Died
29	17 mo	Indefinite	Lobar	+	106	120	34	150 cc	Intramuscular	None given	7	7	7	Normal after first injection cf serum 7 days
30	11 mo		Lobar	+	106	180	55	125 cc	Intravenous	12/29/23 Serum				
								75 cc	Intramuscular	12/30/23 Serum				
								200 cc	Intravenous	1/ 4/24 Serum				
31	14 yr	No history	Lobar	+	104	140	40	100 cc	Intravenous	1/ 8/24 Serum	1	1	1	Normal 24 hr after last Died
32	4 yr	1 day	Lobar	+	104	160	44	300 cc	Intravenous	1/24/24 Serum				
33	11 mo	Indefinite	Broncho	+	101	160	40	200 cc	Intramuscular	1/23/24 Serum	1/2	1/2	1/2	Died in 9 days Died 3 1/2 days after first inj Serum incorrectly given
34	5 yr	6 days	Broncho	+	104	155	40	75 cc	Intramuscular	1/23/24 Serum				
								60 cc	Intravenous	5/ 3/23 Serum				
								110 cc	Intramuscular	5/ 3/23 Serum				
35	9 mo	No history	Broncho	+	101	130	45	200 cc	Intramuscular	5/ 4/23 Serum				Died 5 days Died 9 days after onset Died 22 days after onset
36	7 mo	No history	Lobar	+	102 5	138	40		None given	None given	14	15	15	
37	9 mo	9 days	Broncho	Not made	102	120	60		None given	None given				
38	2 yr	12 days	Lobar	+	104 4	145	65	151 cc	Intramuscular	1/ 7/23 Blood				
39	18 mo	7 days	Broncho	+	102	140	47	235 cc	Intramuscular	1/ 9/23 Blood	2	2	2	Empyema Otitis media on admission
40	3 yr	Indefinite	Lobar	+	103 4	150	48	50 cc	Intravenous	12/ 8/23 Serum	8 hr	1	1	
41	2 1/4 yr	8 days	Lobar	+	102 4	130	40	150 cc	Intramuscular	12/ 8/23 Serum	1	1	1	
42	2 yr	9 days	Lobar	+	105	140	30	400 cc	Intramuscular	2/ 1/24 Serum	3	4	3	
43	2 yr	No history	Broncho	+	102 4	144	40	235 cc	Intravenous	None given	4	1	8	Died ninth day
44	4 yr	No history	Lobar	+	103	126	40		None given	None given	1	1	1	
45	9 mo	No history	Broncho	+	103	130	65		None given	None given				
46	9 hr	No history	Broncho	+	103 8	128	44	265 cc	Intramuscular	12/26/22 Blood	12/30/22	12/26/22	12/27/22	
47	1 yr	12 days	Broncho	+	102 6	120	40	177 cc	Intramuscular	12/30/22 Blood	11	1	18	Died
48	14 yr	Lobar	Lobar	+	104	128	36	350 cc	Intramuscular	1/23/23 Blood	8	2	9	
49	17 mo	No history	Lobar	+	103 2	134	84	100 cc	None given	None given				
								100 cc	Intramuscular	12/ 3/23 Serum				
50	4 yr	4 days	Broncho	+	101	144	40	100 cc	Intramuscular	12/ 4/23 Serum				Died Did not come to normal in hospital
51	11 mo	No history	Lobar	+	105 8	164	54	100 cc	Intravenous	12/ 5/23 Serum				
52	10 yr	No history	Lobar	+	101 2	150	44	100 cc	Intravenous	12/ 5/23 Serum				
53	7 yr		Lobar	+	105	144	36	100 cc	Intramuscular	12/ 5/23 Serum				
54	17 mo	2 weeks before adm	Broncho	+	104 2	150	38	100 cc	Intravenous	12/23/23 Serum	18			Died
									None given	None given	6	6	6	Died 17 days after onset third after admission
55	7 yr	No history	Lobar	Not taken	104	120	30		None given	None given				
56	4 mo	No history	Broncho	—	102	130	47		None given	None given	7	7	7	
57	11 yr	2 days before admission	Lobar	+	104	115	28		None given	None given	6	6	6	
58	9 mo	No history	Lobar	+	104	130	32	400 cc	Intramuscular	2/ 6/23	11	11	11	Died 4 days after admission
59	7 yr	5 days	Lobar	+	104	140	40		None given	None given	4	4	4	
60	2 yr	3 days before adm	Broncho	—	105	144	40		None given	None given	16	16	16	
									None given	None given				
61	7 yr	Indefinite	Broncho	+	105	160	55	100 cc	Intravenous		2 1/2	2 1/2	2 1/2	
62	3 yr	7 days	Lobar	+	105	140	53	100 cc	Intravenous		1 1/2	1 1/2	1 1/2	
63	7 yr	48 hours	Broncho	+	107	150	45	350 cc	Intravenous		3 1/4	1	1 1/2	

was made in using this form of treatment. Some cases receiving serum as well as some that did not were admitted to the hospital in an apparently hopeless condition and died shortly thereafter. It, therefore, seemed that this would make a fair and interesting comparison between those having had the chicken blood or serum and those that did not. Two patients only received serum in which the clinical findings of pneumonia and the type (broncho or lobar) were not first verified by roentgen ray, and in each of these two cases three staff men concurred in the diagnosis. The history of the date of onset was elicited as carefully as possible, but was necessarily questionable in those patients where an illness preceded the pneumonia by several days. Careful white blood counts were made preceding the administration of the serum and daily thereafter in some cases. However, on other cases this work was done by unreliable persons. We have because of this feature decided against including any blood counts in this report. The observation as to the pulse, temperature and respiration were made by reliable nurses.

The blood or serum was given by a staff man or the resident physician. In preparing the serum used, the chicken blood was collected in half gallon jars containing a measured quantity of sodium citrate solution. The serum was removed without pressing the clot. The citrate was removed with calcium and the serum was run through Berkefeld filters. This was then cultured and checked in animals, and if found to be sterile had added to it tricresol and was placed in 100 c c containers with rubber caps.

Sputum cultures were attempted on every patient by catching on a piece of gauze inserted in the throat some of the secretion immediately as it was expelled from the larynx, the results of this we believe to be of no value.

This series includes sixty-three cases, forty-one of whom received either chicken blood or serum. In some of these patients the treatment was given too late in the disease to promise any benefit, in others we now feel the dosage was insufficient or badly distributed. This was necessarily so, since we had no criterion to guide us in our early work. The charts of these cases were carefully reviewed and the points of importance tabulated, as shown in Table 9.

Explanatory remarks on Table 9 are made only where we feel they are required in a given case.

#### ABSTRACT OF CASES

CASE 2—This child had bronchopneumonia as a complication of gastroenteritis and otitis media, he was overwhelmed by these infections.

CASE 3—In this child, whole chicken blood was given, abscesses resulted at the site of injection, which possibly accounts for the continued high temperature, pulse and respiration.

CASE 14—This child developed an abscess from the injection of whole chicken blood, followed by the development of empyema. It would be impossible to tell just where the pneumonia left off and the abscess and empyema began.

CASE 16—This child developed empyema a considerable time after the pneumonia had apparently cleaned up, and died some time later, apparently owing to toxemia and exhaustion. His general condition was very bad from the start.

CASE 17—Death was caused by pneumococcus meningitis, the organism being recovered from the spinal fluid.

CASE 18—This child developed a mild grade erythema multiforme, following the injection of chicken blood, this was an unusual complication in this series of cases. The result was remarkably good considering the amount of blood given.

CASE 27—Lobar pneumonia, complicating measles. Some time later this child developed a pleural effusion and recovered without any further complications.

CASE 30—After the first injection of chicken serum the pulse, temperature and respiration dropped nearly to normal. Three days later an otitis media developed and more serum was given, followed by an immediate response. It would be doubtful whether the serum had much influence in this case, since it ran about the usual duration.

CASE 31—Lobar pneumonia and pyelitis were confirmed by necropsy. This boy was extremely ill and was given 300 c.c. of chicken serum intravenously, and 200 c.c. of the serum intramuscularly, at 1:30 p.m. At 2:10 p.m. a chill developed and the patient went into a state of shock. He died at 3:45 p.m. It is a question whether this death might have been produced by the administration of the serum.

CASE 34—This child was not helped by the serum. The serum used was old and the initial dosage was entirely too small.

CASE 38—This child seemed at first to respond well to the chicken blood serum, but died twenty-two days after the onset of the disease, and twelve days after the administration of the chicken blood. Death was due to extraneous complications.

CASE 42—This child made a good response to the serums. The temperature, pulse and respiration would probably have reached normal earlier had it not been complicated by otitis media which was present on admission.

CASE 47—This child had bronchopneumonia of twelve days duration before admission and showed no response to the chicken blood given. The temperature and pulse required an abnormally long time to reach normal and no complications could be found to account for this.

CASE 49—This case is a very good example of serum badly given. The initial doses were entirely too small for intramuscular doses. The patient showed no response to the serum given and died, although the serum given was fresh.

CASE 50—This patient had only 100 c.c. of serum intravenously. His condition was so extreme that it was not deemed wise to continue its administration. He died a few hours after admission to the hospital.

#### COMMENT

This report covers sixty-three consecutive cases of pneumonia admitted to the ward of the Children's Mercy Hospital, of which seventeen were suffering from bronchopneumonia and twenty-four from lobar pneumonia (making a total of forty-one cases), treated with the blood or serum of chickens. Of these, three bronchopneumonia patients and two lobar pneumonia patients (making a total of five) died. The mortality was 12.2 per cent.

There were twelve cases of bronchopneumonia and ten cases of lobar pneumonia (making a total of twenty-two cases) admitted to the wards during the same period of time, receiving the usual pneumonia treatment, but no chicken blood or serum. Of these, there were seven

bronchopneumonia and one lobar pneumonia patients (making a total of eight) that died. The mortality was 36.3 per cent. The bronchopneumonia patients treated with chicken blood or serum and living required an average of 2.81 days for the temperature, 1.83 days for the pulse and 2.51 days for the respiration to reach normal after the administration of the blood or serum. The lobar pneumonia patients required 1.61 days for the temperature, 1.85 days for the pulse and 1.70 days for the respiration to reach normal after the administration of blood or serum. Of those cases not receiving chicken blood or serum and living, the bronchopneumonia patients required an average of 11.0 days for the temperature, 9.60 days for the pulse and 10.4 days for the

TABLE 10—*Sixty-Five Cases of Pneumonia*

Cases Treated with Chicken Blood or Serum		Total Cases	Total Mortality	Percentage Mortality	
Broncho	Lobar				
17 3	24 2	41	5	12.2	
Cases Not Treated with Chicken Blood or Serum		22 <th rowspan="2">8<th rowspan="2">36.3</th></th>	8 <th rowspan="2">36.3</th>	36.3	
Broncho	Lobar				
12 7	10 1				
Average Number Days for Total Cases to Reach Normal after Use of Chicken Blood or Serum					
Broncho			Lobar		
Temp	Pulse	Resp	Temp	Pulse	Resp
2.81	1.83	2.51	1.61	1.85	1.70
Average Days for Total Number of Cases to Reach Normal without the Use of Chicken Blood or Serum					
Broncho			Lobar		
Temp	Pulse	Resp	Temp	Pulse	Resp
11.0	9.60	10.4	9.44	8.88	9.44

respiration to reach normal after admission to the hospital, at which time they would have received the serum had it been given. The lobar pneumonia patients required 9.44 days for the temperature, 8.88 days for the pulse and 9.44 days for the respiration to reach normal after admission to the hospital. No selection of cases was made for administering the chicken blood or serum. Those patients that did not receive it were either admitted on another service in the hospital or if admitted on our service, there was no serum available at the time.<sup>5</sup>

5 A chill followed the administration of the serum in from twelve minutes in one case to one hour twenty-five minutes in another case, being present in seven of the forty-one patients treated with the blood or serum of chickens. These patients usually required a little more time to reach normal in temperature, pulse, and respiration, and had a slightly longer convalescent period than the average of the others of the series. There was one death among this group, as reported earlier in the paper. We feel that such a reaction is an unusual complication and may be detrimental to a pneumonia patient.

From our clinical experience with the cases just cited, we conclude that in both bronchopneumonia and lobar pneumonia, the mortality can be greatly reduced by the use of chicken blood or serum in addition to the ordinary methods of treatment employed by us, as outlined in our previous communication<sup>1</sup> We conclude also that the convalescent period can be very much reduced by the administration of chicken blood or serum Also that the duration of illness preceding the injection of chicken blood or serum, the age of the serum used, and the dosage given in each individual case are vital factors

We feel that greater possibilities along this line of treatment rest in a more refined method of concentrating the antibodies or by salting out the precipitins, thus decreasing the volume of the dose and the possibility of shock to the patient and facilitating its administration

#### SUMMARY

In summarizing, we give the following as our conclusions

That there is present in the normal chicken serum, a protective substance against the pneumococcus of Types 1, 2 and 3

That this protective substance is not an agglutinin

That agglutinating power can be produced in the blood and serum of chickens by the intraperitoneal injections of live pneumococci, but without increasing the protective power of this serum

That the chicken is tolerant to large doses of pneumococci intraperitoneally with no untoward results

That the protection afforded by chicken serum is inversely proportional to the period of time elapsing between the infection and the administration of the serum

That the protective power of chicken serum, if unpreserved, in time becomes very much attenuated, even if kept under sterile conditions, and may finally become entirely inert

That the protection afforded by normal chicken serum is shared, if at all, to a very much less degree by the other serums employed in these experiments

That in both bronchopneumonia and lobar pneumonia, clinically the mortality can be greatly reduced by the addition of chicken blood or serum to the usual methods of treatment

That the convalescent period in pneumonia can be very much reduced by the administration of chicken blood or serum

That the duration of illness preceding the injection of the chicken blood or serum, the dosage given and the age of the serum used in each individual case are vital factors

That we feel that greater possibilities along this line of treatment rest in a more refined method of concentrating the antibodies or by salting out the precipitins.

## Book Reviews

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### THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR Vol XI Government Printing Office

This volume of 827 pages is devoted to empyema, ophthalmology, maxillo-facial surgery and otolaryngology

The section on empyema is of especial interest to the internist and general surgeon. It is rarely possible to collect and review a series of over 4,000 cases of empyema occurring within a period of less than two years. The epidemiology at each of the various base hospitals is discussed in detail and conclusions drawn from the data so obtained. Twenty-eight pages are devoted to pathology, several excellent colored plates of gross specimens are included. The various methods of treatment such as simple aspiration, thoracotomy and rib resection, are discussed. A very large percentage of the empyemas occurred as a complication of measles or in a severe epidemic of streptococcus pneumonia which invaded a camp during the winter and early spring of 1918. We believe that it is incorrect to consider this streptococcus epidemic as a complication of influenza, as is implied in the report, for the epidemic did not have any of the characteristics of the epidemic in the autumn of 1918. It is also misleading to draw any conclusions on the value of the various measures employed in the treatment of empyema during this streptococcus epidemic, as the virulence of the infecting agent definitely diminished as the epidemic progressed. Any method of treatment instituted late in the course of the epidemic gave a low mortality.

**BASAL METABOLISM IN HEALTH AND DISEASE** By EUGENE F DuBois, M.D., Medical Director, Russell Sage Institute of Pathology, Associate Professor of Medicine, Cornell University Medical College. Pp 372, with index and 79 illustrations. Price, \$4.75. Philadelphia Lca and Febiger, 1924.

This book is successful in the "attempt to bring basal metabolism out of the realm of pure physiology into the domain of clinical medicine." One is impressed by the clarity of exposition of theories, facts and methods, which have been the result of painstaking technical work and thought by many students of this branch of physiology. It is another of the many invaluable contributions by physiologists to clinical medicine. The author has had a very large experience in the clinical application of the tests, and is conservative and reliable in evaluating the results in the diagnosis, prognosis and treatment of disease. He sounds a warning, which is quoted below, because of its soundness and application to other methods of diagnosis now coming into vogue.

"In every disease there is a tendency to variation from the typical which occurs in certain individuals and there are few hard and fast rules in diagnosis. It is very seldom that we should allow any single symptom or laboratory test to outweigh a mass of evidence. A slavish adherence to the basal metabolism test as an index of diagnosis may lead the physician to trouble, first because the test does not always give the true basal metabolism, and second because even the true basal metabolism is not always the indication of the correct diagnosis. God forbid that we make our diagnosis by machinery!"

This is truly a remarkable book.

A DIABETIC MANUAL FOR THE MUTUAL USE OF DOCTOR AND PATIENT By ELLIOTT P JOSLIN, Clinical Professor of Medicine, Medical School of Harvard University Third edition Price, \$2 Philadelphia Lea and Febiger

A new edition of this helpful book will be welcomed by physician and patient as it brings the treatment up to date

To Dr Joslin belongs the credit for emphasizing the importance of educating the diabetic patient From the physician's standpoint, the education of the patient is essential in the treatment of diabetes This book, placed in the hands of the patient, with assistance from the physician, renders the education of the patient a comparatively easy task

Written in a very readable style and yet giving accurate information, it should be valuable to both physician and patient

LEHRBUCH DER KLINISCHEN DIAGNOSTIK INNERER KRANKHEITEN, MIT BESONDERER BERUECKSICHTIGUNG DER UNTERSUCHUNGSMETHODEN Edited by PROF DR PAUL KRAUSE Third edition, revised 502 illustrations Jena Gustav Fischer, 1924

The book is intended to be a guide to the medical student and to the young practitioner It gives a concise review of the methods available to the physician, at the patient's bed and in the laboratory, for the diagnosis of internal diseases

The first part deals with anamnesis and general inspection The interpretation of subjective symptoms is discussed, especially with regard to the misleading localization of pains, and attention is called to the great importance of the constitution to modern medicine A few typical pictures illustrate the influence of disturbances of the glands of internal secretion on the external habitus of the individual

The following sections take up the special findings in different diseases, arranged according to the organs Many good illustrations are added to the text, which is clear and free of unnecessary details Special mention should be made of the colored plates, and the laryngoscopic, cystoscopic and ophthalmoscopic pictures, which are excellent The methods of percussion and auscultation are thoroughly described under the diagnosis of diseases of the respiratory and circulatory systems Short remarks on the physical fundamentals of these methods would facilitate their understanding The irregularities of the heart action are shown by electrocardiographic charts

In the chapter on renal diseases, a description of the chemistry of the blood is lacking The great improvements in the chemical examination of the blood, thanks to the work of Folin, Wu, Benedict, Autenrieth, Bang and others, has made these methods a reliable help indispensable in the modern diagnosis By omitting some of the older methods of merely historical interest, sufficient space could be obtained for a discussion of the chemical composition of the blood in health and disease The few remarks found in the section on diseases of the blood should better have been divided between the diseases of the kidney and the section on metabolism

The average physician probably will not have occasion to make these tests himself as is the case with many other tests described in this book But he should know that the methods exist, and he should be able to judge from the results obtained by them

For testing the renal functions, the methods based on the elimination of normal products of the metabolism under the condition of an increased functional demand (water and concentration test of Volhard) are to be preferred to the injection of dyes

The section on the diagnosis of diseases of the metabolism is almost the shortest one in the book Two pages only are devoted to diabetes mellitus



No mention is made of the acid-base balance, its disturbances and the biochemical methods used to determine them (hydrogen-ion concentration, carbon dioxide combining power)

The general and special diagnoses of the diseases of the nervous system and the diagnosis of the diseases of the blood are among the best parts of the book. The chapters on the diseases of the stomach, intestines, liver, and infectious diseases are short, but quite sufficient. The last part of the book is devoted to roentgen-ray examination.

The book fulfills the purpose for which it was written. It will be a good adviser for the physician during his first years of practice. If the details now lacking should be inserted into a future edition, the book will be one of the best of its kind in the present German literature.

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